Columbia University

Institutional Review Board (IRB)

Policies and Procedures

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Introduction

Columbia University (CU or Columbia) has developed and implemented a comprehensive Human Research Protection Program (HRPP; hereafter referred to as the Columbia HRPP) in accordance with the recommendations in the Institute of Medicine Report entitled Responsible Research: A Systems Approach to Protecting Research Participants (October 3, 2002). The program is charged with the responsibility of ensuring that all human subjects research conducted by Columbia faculty, employees, and students is conducted ethically and in a manner that promotes the protection of human subjects in research. Protections for human participants in all such research must not only be in compliance with state and federal regulations, but must also meet or exceed the standards of accreditation as set forth by the Association for Accreditation of Human Research Protection Programs (AAHRPP).

All human subjects research, whether or not the research qualifies for exemption under the federal regulations, that is conducted by Columbia faculty, staff, or students in connection with their institutional responsibilities must be prospectively approved or determined to be exempt by the appropriately designated IRB under one of Columbia's Federalwide Assurances (FWAs). Per Columbia policy, investigators may not make the final determination of exemption, i.e., protocols which appear to meet federal criteria for exemption from the requirements of the regulations must be submitted to the IRB for confirmation of exempt status.

Throughout these written procedures, "human subjects research" is defined as those activities which meet the criteria articulated in applicable regulations to be considered both "research" and as involving "human subjects".

> Research: a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. [45 CFR 46.102(d)]
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> Human subject: a living individual about whom an investigator (whether professional or student) conducting research obtains
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> (1) Data through intervention or interaction with the individual, or
>
> (2) Identifiable private information. [45 CFR 46.102(f)]

When an activity involves a drug, device, or biological product that is subject to FDA purview, the following definitions also apply:

> Research: FDA has defined *"clinical investigation"* to be synonymous with *"research"*. *"Clinical investigation"* means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA...or the results of which are intended to be later submitted to, or held for inspection

by, the FDA as part of an application for a research or marketing permit. [21 CFR 50.3(c)]

Test Article: any drug (including a biological product) for human use, medical device for human use, human food additive, color, adaptive electronic product, or any other article subject to regulation under the jurisdiction of the FDA. [21 CFR 50.3(j)]

Human subject: an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. [21 CFR 50.3(e)]

The Columbia HRPP covers all entities, offices, and individuals engaged in and/or responsible for the review and conduct of human research at Columbia and New YorkPresbyterian Hospital (NYP). CU has two FWAs: one for Columbia University Medical Center (CUMC) and one for the main campus at Morningside Heights (CU-MS). NYP has its own FWA and is a separate legal entity from CU. Although there are three FWAs, the Columbia HRPP is responsible for all human subjects research conducted at CUMC, CU-MS, and NYP, or by any affiliated faculty, students, or staff of CU and NYP regardless of location. Please see Section IV.A. for the criteria used to determine whether activities conducted by affiliated faculty should be covered by these policies and procedures.

The Columbia HRPP is managed by the Executive Director, Human Research Protection Program (ED), who is also responsible for the management of all Institutional Review Boards (IRBs) at CU. Sections I and II of these written procedures outline and summarize the Columbia HRPP.

The Columbia research enterprise is extensive in its size and broad in its scope and nature of activities, including biomedical, behavioral, and epidemiological research, as well as studies in the area of health services. Subjects may include healthy volunteers, as well as patients, and other individuals who may be considered vulnerable due to medical, cognitive, emotional, economical, educational, age, or other factors. Although much of the research is conducted in the New York City area and on Columbia campuses, faculty members also actively conduct research at other sites both domestic and international. Furthermore, many Columbia faculty members collaborate on projects with investigators at other institutions. The Columbia HRPP accounts for approximately 1,400 new human research studies each year.

To facilitate management, review, and oversight of its research enterprise, Columbia has developed an electronic submission system called RASCAL. The RASCAL system requires that all research proposals be submitted in the system for review by the IRB and other administrative offices. This system provides a high level of accountability for all research protocols, as it allows for tracking of research, systematic administration of reviews by the IRBs and other committees, processing and accounting of human research educational training, and management of conflicts of interest.

I. Institutional Leadership

The Columbia HRPP reports to the Executive Vice President for Research (EVPR) and the Institutional Officials designated on the FWAs of CUMC, CU-MS, and NYP. The EVPR, reporting directly to the President of the University, has overall responsibility for the University's research enterprise. The Office of the EVPR establishes and administers the policies governing the conduct of research at the University and oversees the management of its research programs. In 1966, Columbia established its first IRB under the authority of H. Houston Merritt, then Dean of the College of Physicians and Surgeons of Columbia University. Because of changes to the University administrative structure since 1966, including centralization of administrative functions and the establishment of the Office of the EVPR, the functions of and charge to the IRB are now under the purview of the EVPR.

The EVPR is responsible for central oversight of the entire Columbia HRPP and also serves as the Institutional Official (IO) on the FWA for CU-MS. Each IO is responsible for ensuring that all research under his/her FWA is conducted ethically and in compliance with all regulatory standards. The EVPR, together with the IOs of CUMC and NYP, the Vice President of Research Operations (VPRO), and the ED provide a team approach for oversight of the protection of human subjects in research.

Essential to the success of the Columbia HRPP is the institutional culture or conscience that permeates all components of the program. Research is one of the key missions of Columbia, which prides itself on its commitment towards excellence in all research activities. Columbia and NYP recognize that the ethical conduct of research is not only vital for the success of the research enterprise and the public trust of surrounding communities in our research programs, but more importantly that the institutions have a moral responsibility to act accordingly. Towards these ends, the EVPR and the IOs of CUMC and NYP lead the Columbia HRPP in many different ways, including: 1) instilling the above described culture; 2) supporting the Columbia HRPP with the necessary funds, resources, and intellectual support; and 3) providing the necessary authoritative leadership and support for ensuring the integrity of Columbia's program for the handling of alleged noncompliance incidents.

II. IRB Office

The IRB Office is the central administrative office for the Columbia HRPP. This office serves as the central repository of all information affecting the protection of human subjects in research. The IRB Office is responsible for the management and oversight of all IRBs at CU-MS and CUMC, as well as the reporting of all safety and noncompliance issues regarding research involving human subjects. In addition, the IRB Office is responsible for ensuring that all relevant information affecting the safety and welfare of human subjects in research is reported to the IRBs, and as appropriate to the IOs, federal regulatory agencies, sponsors, and AAHRPP. The IRB Office has two locations: a) on the CUMC campus, on the fourth floor of the Mailman School of Public Health building, and b) on the CU-MS campus, (see Working Practice Document #160, IRB Contact Information, for current address).

The IRB Office leads quarterly meetings with the heads of all Columbia HRPP units involved in the administration and conduct of human research. The purpose of these meetings is to ensure coordination and communication of policies and issues relevant to the protection of human subjects in research. In addition, the IRB Office convenes ad hoc meetings as necessary to address any incidents or issues that may require additional consideration or more immediate action. As necessary for prompt notification, the IRB Office sends electronic communications of relevant information regarding the ethical conduct of human research and the protection of human subjects to all heads of Columbia HRPP units.

The IRB Office also leads semi-monthly meetings with the Executive Committee of the IRB. This Committee is comprised of the Chairs and Vice Chairs of all four IRBs, the VPRO, the Associate Director, IRB (AD), and the ED. The purpose of these meetings is to improve the quality and consistency of the work performed by the four IRBs and to address overarching issues and challenges that may face all IRBs. Once a month, all IRB officers also attend this meeting.

Five other committees support initiatives to improve the ethical conduct and review of research: 1) Education and Training Committee, 2) Policy Committee, 3) Accreditation Committee, 4) RASCAL Committee. The purpose of each committee is discussed in more detail below. Additional committees may be constituted as necessary to support office initiatives.

A. Institutional Review Boards

There are four IRBs (commonly referred to as "Boards") in the Columbia HRPP. Three IRBs are responsible for review of human subjects research conducted by faculty, employees, staff, and students at CUMC and NYP and one IRB is responsible for human research conducted by faculty, employees, staff, and students at CU-MS. Additional IRBs may be added as necessary to ensure adequate and timely review of research proposals submitted for consideration.

All CU IRBs are governed by the principles of the Belmont Report and the federal regulations for the protection of human subjects in research as codified by:

1. the U.S. Department of Health and Human Services (HHS) regulations, 45 CFR Part 46, Subparts A (Common Rule), B, C, and D (Appendix VI);
2. the U.S. Food and Drug Administration (FDA) Regulations, 21 CFR Parts 50, 56, 312, 600, and 812 (Appendix VII);
3. the Department of Education Family Education Rights and Privacy Act (FERPA);
4. New York State Laws 2440/441 and Article 7, Section 79-1 (Confidentiality of Genetic Tests);
5. Columbia institutional policies; and
6. the AAHRPP Accreditation Standards.

All CU IRBs are charged with the responsibility of providing review, approval, and oversight monitoring to ensure that all human research under the auspices of the Columbia HRPP is conducted: 1) ethically; 2) in a manner that protects human subjects, and 3) in accordance with the above mentioned regulations, laws, policies, and standards.

The mission of the CU IRB is to enhance and facilitate the ethical conduct of human subjects research conducted by Columbia, and by Columbia faculty, regardless of location. The CU IRB will perform this mission through its review of human subjects research, its educational and training initiatives, and its compliance oversight and quality improvement programs.

The IRBs are not solely responsible for the integrity and conduct of such research, nor for the programmatic development or decisions as to what research should or should not be conducted at Columbia. These considerations also fall under the purview of the Dean's Office for CUMC, the Chief Medical Officer for NYP, and the EVPR, who have the authority to restrict research that cannot be supported by resources, principles, or policies of the respective institutions, regardless of whether it has been approved by one of the CU IRBs.

The IRBs act independently and consider research proposals from the perspective of protection of the subjects who may be involved. While approval from other CU offices or committees may be necessary per institutional policy, the decision of whether to approve or disapprove a submission is made autonomously and is not influenced by potential funding, prestige, or other benefit that may accrue to the University. Minutes that document IRB actions are routinely forwarded to the Institutional Officials, representing CUMC, CU and NYP, for consideration of whether they may appropriately be conducted under the auspices of these institutions.

The Boards are subject to regulation by federal oversight agencies, including the FDA and the Office for Human Research Protections (OHRP). Other federal, state and local agencies may have authority to oversee specific aspects of individual research projects or the research program in general.

There are four teams of staff that provide administrative support for the IRBs. Each IRB has its own dedicated team. In addition, the Compliance Oversight Team and the Central Review Team provide administrative support to each of the four IRBs, as described below.

B. External IRBs

CUMC and NYP, collectively, have IRB Authorization Agreements with the Western IRB (WIRB), the New York State Psychiatric Institute's (NYSPI), the Weill Medical Center of Cornell University, the National Cancer Institute Central IRB (CIRB), the National Cancer Institute Pediatric Central IRB, CU-MS, and the Biomedical Research Alliance of New York (BRANY) to rely on reviews by their IRBs for certain types of research projects. Details regarding each agreement are provided later in this manual.

The decision to enter into an agreement with another institution for reliance of both institutions on one of the IRBs is made after: a) evaluation of the non-CU institution's IRB policies and procedures (when CU will delegate review); b) consideration of whether regulatory compliance and CU standards may be upheld through the relationship; c) analysis of whether an efficient process may be implemented to conduct the reviews; d) discussions between IRB administrators from each institution; and e) consultation with the CU Office of the General Counsel. The CU IRB management meets on an ad-hoc basis with representatives from each external IRB to consider issues relevant to the review of human subjects research at Columbia.

C. IRB Staff Teams

Each IRB is administered by a team of staff composed of an IRB Manager, Assistant Manager or Board Coordinator, and one or two administrative support staff. Each team is responsible for ensuring that all research reviewed by its IRB is in compliance with all above-referenced standards and that all reviews are handled efficiently and at a high level of quality. Each team is responsible for preparing its IRB with the necessary information to conduct its reviews and to process all communication to the research team.

D. Central Review Team

The Central Review Team (CRT) handles the initial receipt of research studies for IRB review and triages these studies for an initial pre-review by IRB staff, followed by a review by one of the four CUMC IRBs, or CU-MS, as appropriate. Each incoming new study receives a thorough pre-review by IRB staff utilizing a detailed pre-review form. The pre-review process is designed to help ensure that each study is submitted with the necessary information to proceed for IRB review and that each study will receive all relevant regulatory considerations. Once a study has received a pre-review it is assigned to an IRB for review.

The CRT is responsible for conducting pre-reviews of all continuing review requests, and all modifications or amendments, submitted to the CUMC IRBs for approved research studies. The pre-review of continuing review submissions also utilizes a pre-review form to ensure that the necessary information is submitted. This pre-review includes a quality assurance assessment of the study for the most recent approval period to ensure that all prior actions were appropriately handled and that any outstanding items will be addressed at the upcoming IRB review. If there

has been a lapse in IRB approval or an indication that the study is not proceeding as planned, the review may cover a longer period. Pre-review of modifications or amendments is also done, in order to prepare the IRB for its review of these submissions.

The CRT conducts a pre-review of all reports of unanticipated problems involving risks to subjects or others that are submitted to the CUMC IRBs. The pre-review ensures that these reports meet the CU Reporting to the IRB of Unanticipated Problems policy and cases are identified that require immediate attention. For such reports that satisfy Columbia's individual event reporting policy, the CRT staff conducts the preliminary review and makes a recommendation about whether the informed consent document and/or protocol require revision. Reports of events that do not meet the criteria for individual submission are returned without review.

CU-MS IRB staff conduct the pre-reviews for renewals, modifications, and reports of unanticipated problems submitted for protocols reviewed by the CU-MS IRB.

E. Compliance Oversight Team

The Compliance Oversight Team (COT) is responsible for investigating and handling all allegations of noncompliance, concerns about research conduct, and complaints with respect to the protection of human subjects in research. Allegations of noncompliance, concerns, or complaints may be received from IRBs, faculty, research staff, IOs, departmental administrators, research subjects, federal and state regulatory agencies, the media, or the general public. All allegations of noncompliance, concerns, or complaints, as well as any other event that must be reported to federal regulatory agencies (e.g., unanticipated problems, suspension of IRB approval) are logged into a tracking system by the COT, which promptly notifies the ED of such reports (if the ED has not already been advised of the allegation).

Alleged incidents of noncompliance are handled in accordance with the Columbia Noncompliance with Human Subjects Regulations Policy. When a determination of noncompliance has been made an appropriate corrective action plan is developed. A follow-up report of serious or continuing noncompliance is then filed with the respective IRB, the appropriate IO(s), the EVPR, and when appropriate, with the relevant regulatory agency and sponsor.

The COT will also conduct not-for-cause audits as part of the IRB's compliance oversight initiatives.

F. Education and Training Committee

The Education and Training Committee, one of several standing committees established in 2003 within the IRB office, holds regular educational sessions for IRB staff, members of the CU research community, and IRB members. The Committee meets at least monthly and is chaired by the AD. Committee membership is comprised of IRB staff, each of whom contributes to an

active, year-round schedule of events that includes monthly IRB-investigator meetings, an annual IRB conference, "IRB 101" sessions for researchers, RASCAL training sessions for IRB members, orientation for new IRB members, and staff training sessions on a variety of topics.

Efforts by staff to expand their knowledge of the ethical and regulatory bases for human subject protection by completing online tutorials, attending local and national conferences, and obtaining Certified IRB Professional status are strongly encouraged. Educational training activities for staff include both mandatory and voluntary initiatives.

G. Policy Committee

The Policy Committee, also established in 2003 within the IRB Office, is responsible for the formulation and drafting of policies related to: 1) the ethical conduct of human research, 2) the protection of human subjects in research, and 3) IRB review and processes. The Committee meets at least monthly and is chaired by an officer on the IRB staff or the ED. Committee membership is comprised of IRB staff and the Policy Advisor to the IRB, who is the Director, Center for Bioethics. The VPRO serves as an ad-hoc member.

H. Accreditation Committee

The Accreditation Committee was established in 2004 within the IRB Office and is charged with preparation for and maintenance of accreditation of the Columbia HRPP. The Accreditation Committee also has the authority to develop and draft new IRB Policies and Procedures or IRB processes that generally do not have broader implications (e.g., policies that do not also impact the investigators). The Committee is charged with the added responsibility and authority for the monitoring and oversight of internal IRB processes so that accreditation can be obtained and maintained.

I. RASCAL Committee

The RASCAL Committee was established in 2004 within the IRB Office and is charged with working with the RASCAL Information Technology (IT) Team for further development and enhancement of the RASCAL system as it relates to the IRB module. The RASCAL Committee is the central repository of all suggestions for improvement of the IRB module. The Committee is responsible for prioritizing all requests for RASCAL improvements with the input of the four CU IRB Chairs and staff. Meetings are held on an ad hoc basis as necessary to accommodate the current needs of the RASCAL system and evaluate any new processes being tested. The Committee is chaired by an officer on the IRB staff.

J. Privacy Board

The Columbia University IRBs also serve as the Privacy Boards for the review protected health information that may be used by Columbia investigators and for ensuring the compliance with the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996. The implementation of policies and processes to ensure such compliance will be the responsibility of the Privacy Officer who reports to the Office or Research Billing Compliance. The Privacy Officer will coordinate such efforts with the ED and AD of the IRB. See Working Practice Document #115 (Columbia University Institutional Review Board Policy on Research and the HIPAA Privacy Rule) and Working Practice Document #116 (Columbia University Medical Center Institutional Review Board Procedures to Comply with Privacy Laws that Affect Use and Disclosure of Protected Health Information for Research Purposes).

III. IRB Policies and Procedures

A. Development

Columbia University has adopted these IRB written procedures to ensure the ethical conduct of research and protection of the rights and welfare of human subjects participating in research conducted under the authority of the University. This document describes the means by which research with human subjects will be reviewed, approved, and monitored.

The Boards have adopted these written procedures to comply with the U.S. HHS Regulations on research with human beings (Appendix VI), and the U.S. FDA regulations on research with human beings (Appendices VII). To the extent consistent with federal law & regulations, the written procedures comply with the International Conference on Harmonization (ICH) "Guidance for Industry- E6 Good Clinical Practice: Consolidated Guideline" (Appendix VIII).

Policies and procedures are developed within the IRB by one of the two standing committees described in Section II: the Policy Committee or the Accreditation Committee.

The IRB Policies and Procedures will be reviewed regularly, and minimally once per year. Any necessary revision to these policies must be made through the process described in the following section.

B. Process for Revising Policies and Procedures

1. The proposed revision must be submitted to either the Policy or Accreditation Committee for consideration.

    a. More significant changes that may have broader implications should be handled by the Policy Committee.

    b. Minor or less significant changes should be handled by the Accreditation Committee.

2. If necessary, the Chairs of each Committee will discuss jurisdiction of any proposed revision and make a decision as to which Committee will consider the revision. The ED will have the authority to make the final decision.

3. Once a proposed revision is considered by either Committee, a draft will be forwarded to the ED, the AD, all IRB Chairs, the VPRO (when appropriate), and staff for review and consideration. After a one week review, all comments will be considered by the Committee that drafted the proposed revision.

4. If no substantive change has been made during the one week review period, the final draft version will be forwarded to the ED for approval. Approval of revised policies will be indicated with the date and signature of the ED.

5. If substantive changes have been made during the one week review period, a revised version will again be circulated to the IRB Chairs and staff for a one week period. This process may continue until the final revised policy is approved. The ED has the authority to revise and approve the policy at a point when all remaining concerns are editorial or grammatical.

6. Approved policies and changes to these written procedures will be posted on the CU IRB websites. Appropriate individuals (e.g., research personnel, IRB staff, IRB members and Chairs, VPRO, IOs, EVPR) will be notified of new policies and changes to these written procedures.

Revisions to the policies may be made on a section or item basis. This process will allow more timely updates to the policy rather than requiring re-approval of the entire set of IRB Policies and Procedures with each revision.

Proposed revisions may be forwarded to any of the IOs or the Columbia Office of General Counsel for consultation and input.

At the discretion of the ED, or the AD, any change to these procedures may be implemented immediately without following this process if a determination is made by the ED or AD that the change is necessary for the immediate protection of human subjects or to address an urgent regulatory compliance concern.

IV. Scope of Authority

The Boards have the responsibility and the authority to:

- review all human subjects research described in Section IV.A. for prospective IRB approval;
- review progress of studies at least yearly and more often when deemed necessary;
- observe or have a third party whom the Boards determine is qualified and appropriate observe the consent process or any aspect of the research;
- suspend or terminate approval of any study that has an unanticipated problem involving risks to human subjects or others, serious or continuing noncompliance with any federal regulation, or serious or continuing noncompliance with the requirements or determinations of the IRB. Such actions will generally be determined at a convened meeting of the full Board with a quorum present and will be incorporated into the minutes of the meeting. However, an IRB Chair, the ED, or the AD (in the absence of the ED), may suspend any study outside of an IRB meeting if new information regarding risks becomes available or it is otherwise determined to be in the best interest of the subjects;
- restrict any study it determines to warrant such action. If one aspect of a study fails to comply with federal regulations or Board requirements or determinations, the Boards may restrict the study;
- review research that was initiated without IRB approval for compliance with federal and state regulations and/or institutional policy.

CU IRB approval is required before implementation of any research involving human subjects, including review of records, tissues, or other derived materials.

A. Research Conducted by Investigators Affiliated with Columbia

Under the terms of the FWAs, CU has given the Boards the authority to protect all human subjects involved in research that is conducted by investigators who are affiliated with Columbia, and in all other activities which even in part involve such research, regardless of sponsorship, if one or more of the following apply:

1. the research is sponsored by this institution (CU);
2. the research is conducted by or under the direction of any employee or agent of this institution, in connection with his or her institutional responsibilities;
3. the research is conducted by or under the direction of any employee or agent of this institution using any property or facility of this institution; or
4. the research involves the use of this institution's nonpublic information, e.g., to identify or contact human research subjects or prospective subjects, for data review or analysis.

"Agent" in the preceding statements is defined as an individual or entity that has an agreement with the University to perform specific tasks or provide defined services and is not an employee.

Columbia University may enter into an IRB Authorization Agreement (IAA) with other FWA entities to delegate IRB review to another designated IRB. Prior to executing in which Columbia will rely on the review of another IRB, the ED or designee will determine that the quality of their reviews is appropriate for Columbia's HRPP, and the reviewing IRB complies with applicable federal and state statutes in their reviews and operating procedures. These determinations may be made through various means, including review of operating procedures, attendance at IRB meetings, discussions with IRB administrators, and assessment of whether federal regulatory agencies have restricted or suspended the IRB's operations.

Any Columbia faculty, employee, staff, student or agent that conducts human subjects research must obtain prospective approval from the appropriately designated IRB under the Columbia FWAs prior to the initiation of such research. All human subjects research that qualifies for exemption under the federal regulations must also be submitted to the appropriately designated IRB for confirmation of the exempt status.

B. Research Conducted at CU by Investigators Affiliated with Other Institutions

Columbia University officials and faculty are often approached by investigators at other institutions for cooperation in their research. In addition, investigators at other institutions may propose a study to be conducted, all or in part, on a CU campus.

The need for review by the CU IRB will depend upon the nature of the involvement of the individual who is affiliated with CU in the former situation, and the proposed use of CU facilities, resources, and/or non-public data in the latter circumstance. Therefore, a description of the research that is proposed should be submitted to the ED or AD for administrative review and a determination as to whether CU IRB review is also needed (if the researcher does not want to seek this determination via a RASCAL submission).

CU IRB review is not generally required if, in the case of proposed collaboration, the individual who is affiliated with CU is not engaged in human subjects research, i.e., the individual will not: a) intervene or interact with living individuals for research purposes; b) obtain individually identifiable private information for research purposes; or c) receive a direct federal award. For example, department Chairs or Deans may be asked to assist in the distribution of surveys to faculty or students. IRB approval is not required for university offices or officials to inform members of the university about research or provide them with information about contacting investigators if they wish to participate. A detailed explanation of when an institution is engaged in research can be found in the OHRP October 16, 2008, "Engagement of Institutions in Research", which provides the basis for the Columbia engagement philosophy and can be found online at <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>.

CU IRB review of research by investigators from other institutions is generally required, (i.e., the research falls under the jurisdiction of the CU IRB), if:

1. University officials, faculty, staff, or students are actively engaged in or actively cooperate with or encourage participation in the research;
2. University officials, faculty, staff, or students intend to use the findings or results of these studies for their own purposes;
3. Private, confidential information about members of the Columbia University community will be released for purposes of the research; or
4. The research is sponsored by Columbia University.

For those protocols that require review by the CU IRB, submission in RASCAL is required.

The ED serves in an advisory capacity to university officials and faculty with regard to research conducted by investigators from other institutions at Columbia University that does not fall under IRB jurisdiction (i.e., the ED can provide advice on such matters as the risks and benefits of the proposed research, informed consent, etc.).

C. Research Investigators

A Columbia University faculty Officer of Instruction, with a full-time appointment at the rank of instructor or higher may serve as a Principal Investigator (PI) on a protocol. Full-time Officers of Research at the rank of Research Scientist (or equivalent) or higher may also serve as a PI. Exceptions will be considered by the appropriate authority on the relevant campus (Working Practice Document #13). Criteria for serving in the role of PI are determined by the institution and articulated in the Principal Investigator Eligibility policy.

A student may not serve as the PI on a protocol. Appropriately qualified students may have a substantial role in a research project, but supervision by a faculty advisor is required. In most cases, the faculty advisor also serves as the PI for the project.

The PI has ultimate responsibility for his/her research project and all official hard copy IRB correspondence is addressed to the PI. RASCAL correspondence is sent to the PI as well as those members of the research team designated per RASCAL procedures (Working Practice Document #95). Responsibility for the ethical conduct of all study procedures conducted under the auspices of Columbia University, from initial recruitment efforts, through completion of data analysis, rest with the PI, who may delegate tasks but retains responsibility for them.

No studies involving human subjects may be conducted without IRB approval, IRB determination of exempt status in accordance with 45 CFR 46, or determination that the regulatory definitions of both "research" and "human subject" are not met (i.e., "Not Human Subjects Research"). Although a PI may make a determination of "Not Human Subjects Research" on his/her own, without submission to the IRB, if that decision is incorrect, the PI will be responsible for any noncompliance that results. Consultation with IRB staff or submission of the protocol to the IRB via RASCAL is recommended whenever it is not clear whether the regulatory definitions of "research" and "human subject" are met.

Before a protocol will be approved by a CU IRB, the PI must review the most pertinent Good Clinical Practice (GCP) or Human Subjects Research course offered by Columbia and receive a passing score of 80 or greater on the relevant exam. Research personnel other than the PI who have contact with subjects, contact with confidential study data, or are otherwise engaged in the research (i.e., key personnel) must also complete training in the protection of human subjects prior to participation in the research.

Key personnel on the CUMC campus must also complete the CUMC online HIPAA (Health Insurance Portability and Accountability Act) training course prior to participation in the research. If a protocol submitted by faculty from the CU-MS campus involves the creation, use, or disclosure of PHI, completion of the HIPAA training course is also required.

If the study population includes children, completion of the online Collaborative IRB Training Initiative (CITI) Biomedical Research with Minors module is required. The CITI course is managed by the University of Miami and may be accessed at: http://www6.miami.edu/citireg/.

Evidence of GCP, Human Subjects Research, and HIPAA certification is maintained electronically within the RASCAL system.

D. Organization and Membership of the Boards

The system of human subjects protection at Columbia functions with the number of IRBs necessary to conduct quality and timely reviews of all human subjects research. Columbia will periodically evaluate the number of Boards, and their composition, and make the necessary modifications, including constitution of additional Boards, to ensure adequate review.

Each IRB will ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable laws, and standards for professional conduct and practice.

Once a Board has reviewed a protocol, all additional oversight and actions will, whenever feasible, be performed by that same Board (i.e., continuing review, review of modifications, and unanticipated problem considerations). The Board will delegate compliance oversight activities to the COT for purposes of conducting investigations, in accordance with the Compliance Oversight policy, but will receive and act on the COT reports as discussed in Section IX.

Each Board will be distinct and completely separate from the other Boards in that it will act independently on protocols assigned to it. If an issue affects more than one Board (e.g., an investigator with studies open under more than one Board is failing to comply with regulations), each Board will address the issue separately or collectively, i.e., as the Executive Committee, at the discretion of the Chairs, the ED, and/or the Executive Committee.

Each Board has its own chairperson. The Chairs on the CUMC campus are administratively responsible to the Senior Vice Dean of the Faculty of Medicine, College of Physicians and

Surgeons (”IO-CUMC”) at CUMC and the EVPR; the Chair on the CU-MS campus is administratively responsible to the EVPR. The Chairs have direct access to the EVPR, IO-CUMC (as applicable), and to the CU President for discussion of IRB issues.

The EVPR is responsible for providing adequate support and resources for the overall operation of the IRB. Coordination of Board activity is achieved by the Executive Committee.

1. Membership

The Columbia IRBs are comprised of three non-specialized Boards on the CUMC campus, one specialized Board on the CUMC campus (oncology), and one non-specialized Board on the CU-MS campus, each of which meets an average of two times per month. Each Board is constituted to meet the regulatory requirements mandated by HHS and FDA, and institutional needs, i.e., individuals with the necessary expertise to evaluate the type and volume of protocols submitted for review.

2. Qualification of Members

The membership of each Board includes individuals with varying backgrounds, who possess the appropriate professional competence to review the diverse types of protocols that are received, or provide awareness of considerations of the local community. Both genders are represented and cultural diversity is supported.

Each IRB includes among its membership at least one individual who has no affiliation with CU (and no immediate family member with an affiliation with CU) other than his/her IRB membership and at least one scientist. There is at least one voting member at every meeting whose interests and background are primarily non-scientific (lay person). One IRB member may fulfill both criteria. In addition, each Board that reviews FDA-regulated products (drugs, biologics, and devices) has at least one member present who is a physician. A prisoner advocate is on the roster for each Board, either as a full member or as an alternate who counts towards quorum and as a voting member for prisoner research only.

3. Membership Diversity

Membership is selected to assure appropriate diversity, including representation by multiple professions, multiple ethnic backgrounds, and both genders, and to include both scientific and non-scientific members.

4. Alternate Members

One or more alternate members exist for key members of each IRB. Such alternate members must be of the same category of membership (i.e., scientific or non-scientific), and meet the afore-mentioned guidelines.

5. Use of Consultants

The Boards may, at their discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the Boards. These individuals may not vote with the Boards.

Consultants will be required to sign a Confidentiality/Conflict of Interest Statement (Working Practice Document #76). Conflict of Interest parameters, including definitions of "financial interest" and "family member", may be found in the University Policy on Financial Conflicts of Interest and Research (Working Practice Document 219 and posted online at: http://evpr.columbia.edu/files_sponsoredprojectprocedures/imce_shared/COI_Policy_with_eff__date_7_1_09.pdf

A consultant who has a conflict of interest must leave the room during the Board discussion and vote. The Board may ask the consultant questions related to the protocol prior to completion of the discussion, after which the consultant will leave the room for the remainder of the discussion and vote.

When consultants are utilized, the terms of the service that will be provided, description of deliverables (e.g., written report, verbal presentation, review of investigator responses), and explanation of confidentiality agreements (e.g., whether name of consultant will be provided to the PI, whether the consultant's report will be released to the PI, whether the PI may contact the consultant) should be documented in writing.

Consultants will usually be identified by Board members or IRB staff, although in some cases, the PI or his/her department may be asked to suggest an individual with appropriate expertise. A list of consultants will be maintained by the IRB office.

E. Appointment and Terms of IRB Chairs and Members

The ED and the AD are responsible for the management of all CU IRBs and the IRB office staff. Oversight of the performance and management of all CU IRBs is delegated to the AD. Each IRB Chair, and IRB Manager, are responsible for daily management of their respective Board.

1. Chair/Vice Chair

a. Selection and Appointment

The IO listed on the FWA will appoint the Board Chairs, after consultation with the ED. CU faculty who are Officers of Research or Officers of Instruction, and have sufficient expertise and experience, will be considered for these IRB positions. Other experienced IRB members will be considered on a case by case basis, taking into account their expertise and suitability for the position. A curriculum vitae will be required upon appointment, and a request for an updated version will be made periodically by the IRB.

An appointment memo is prepared by IRB staff for approval and signature of the appropriate IO. Copies of the signed memo are sent to appropriate individuals, including the IO, respective IRB Chair and Vice Chair, ED, AD, and Manager of the relevant IRB. A copy is retained in the IRB member file.

An appointment letter is generated, signed by the ED, and sent to the appointee. Copies are sent to appropriate individuals, including the IO, respective IRB Chair and Vice Chair, ED, AD, and Manager of the relevant IRB. A copy is retained in the IRB member file.

b. Length of Term/Service

The Board Chair will be appointed to serve a three-year term, which may be renewed. The terms correspond with the fiscal year (July 1 to June 30). If a Chair is appointed mid-year, his/her term will be calculated from the following July 1st. The IO and the ED, considering input from Board members, investigators, and other administrators, will evaluate the Chairs on a regular basis (see Working Practice Document #113 for process) and renew terms accordingly. Shorter terms may be considered in special circumstances.

In accordance with the "Recognition of Service by IRB Members" memo (Working Practice Document #109), IRB Chairs will receive a token of appreciation upon completion of their service, or as otherwise determined.

c. Duties

Each Board Chair has the responsibility to ensure the compliance of the Board with all federal regulations, and manages his/her review Board and the matters brought before it according to HHS and FDA regulations pertaining to the rights and welfare of research subjects.

Each Board Chair is responsible for conducting the Board's meetings, as well as processing submissions to his/her respective IRB in RASCAL**.** Assignment of primary reviewers and distribution of submissions to those reviewers is performed by the Chairs. Decisions to use consultants when specific expertise is not available among Board members are made by the Chair, generally in consultation with the respective Manager. The signatory responsibility for IRB correspondence is designated by the Chair, in accordance with IRB policies (see Section V.H.1).

A Vice Chair will be appointed for each Board, and will run the meeting and process submissions in the absence of the Chair. In the event of the temporary and short term absence of both the Chair and the Vice Chair, an experienced IRB member will be selected by the ED or designee (e.g., AD, or Chair with concurrence of the ED) to serve in this role. An IRB may have more than one Vice Chair; a hierarchy for serving as Acting Chair in the absence of the Chair will be established when there is more than one appointed Vice Chair.

d. Resignation/Removal

Prior to the start of each fiscal year, the EVPR and/or respective IO, in consultation with the ED, may determine that the appointment of any Chair whose term is expiring should not be renewed.

Resignation from the Board may occur at the end of a term or mid-term. Notice should be provided to the relevant Chair and ED as far in advance as possible to facilitate identification, appointment, and training of a qualified replacement.

After consultation with the ED, the EVPR or the IO designated on the applicable FWA may remove a Chair mid-term (i.e., at any time during the appointed term).

Individual termination letters are prepared by IRB staff and signed by the IO. Once signed, copies are distributed to appropriate individuals, including the IO, respective IRB Chair, ED, AD, and Manager of the relevant IRB. A copy is retained in the IRB member file.

e. Education and Training

Chairs are expected to participate in initial (i.e., one or more orientation sessions) and continuing education initiatives to understand, and keep abreast of, changes to institutional policy, relevant legal statutes, the RASCAL system, and evolving interpretation of regulations, policies, and laws. Details of education and training initiatives are provided in Section X.

f. Liability Coverage for IRB Chair/Members

IRB Chairs are protected from personal liability under the Columbia insurance policy, which protects individuals serving on all University committees.

g. Confidentiality/Conflict of Interest Statement

All Board Chairs are required to sign a Confidentiality/Conflict of Interest Statement (Working Practice Document #76), the concepts of which, in regards to conflict of interest, are reinforced during the orientation session for new members. The statement also articulates the need and expectation for Board deliberations and details of the protocols that are submitted to the IRB to remain confidential.

Chairs who have a conflict of interest with a particular protocol, event, or issue that is reviewed by the Board are expected to recuse themselves from relevant Board deliberations and votes.

1) For convened meetings, this means that the Board member must leave the room during the Board discussion and vote; the conflicted member will not count towards quorum for that review. The Board may ask the conflicted member questions related to the protocol prior to completion of the discussion. IRB staff, during preparation of the agenda for full Board meetings, will identify those submissions for which a Board member who is expected to be in attendance for the meeting has a conflict; this helps to ensure

compliance with the need for any such members to leave the room during discussion of the protocol for which a conflict exists.

2) In the case of expedited reviews, a Board member who has a conflict of interest in relation to a specific protocol is expected to notify the Chair if a submission for that protocol is assigned to the member for review. IRB staff who conduct the administrative review and identify a conflict will include that information in the Notes for the protocol.

1) For both full Board reviews and expedited reviews, the RASCAL system will not allow an individual who is named among study Personnel on a submission to be assigned as a reviewer for that submission.

2) Whenever possible, IRB staff will not assign a protocol, for which an IRB member is the PI, to the IRB on which the PI is a member.

Conflict of Interest parameters, including definitions of "financial interest" and "family member", may be found in the University Policy on Financial Conflicts of Interest and Research (Working Practice Document 219 and posted online at: http://evpr.columbia.edu/files_sponsoredprojectprocedures/imce_shared/COI_Policy_4_3_09_new.pdf).

2. IRB Members

a. Selection and Appointment

The Chairs and/or IO, in consultation with the AD (and ED when necessary), recommend candidates for appointment as IRB Board Members and the IO named on the FWA makes the appointment to the Board via signature on an appointment memo. Members will be selected in a manner that will ensure that all requirements of these IRB procedures and federal regulations are met. A curriculum vitae, which is generally reviewed during the recruitment process, will be required upon appointment, and a request for an updated version will be made periodically by the IRB.

A letter of appointment is prepared by IRB staff for approval by the appropriate IO. This letter can be signed by either the ED, or by the relevant IO.

Upon being signed, copies of the appointment memos and letters are distributed to appropriate individuals, including the IO, respective IRB Chair and Vice Chair, ED, AD, and Manager of the relevant IRB. A copy is retained in the IRB member file.

b. Length of Term/Service

Members are appointed to a term of up to three years, which may be renewed, and will be evaluated periodically (see Working Practice Document #114 for process). Board Members may

be granted an extended leave due to medical, personal or professional reasons, then return to complete their term.

In accordance with the "Recognition of Service by IRB Members" memo (Working Practice Document #127), IRB members will receive a token of appreciation upon completion of their service, or as otherwise determined.

c. Duties

Members independently evaluate project submissions that require full Board review prior to the IRB meeting, participate in appropriate discussions, and vote to approve, disapprove, defer to Chair (i.e., require specific changes, RASCAL status "pending"), defer to Board (i.e., substantive revision required, RASCAL status "return"), or defer (table) each submission during the IRB meeting. These actions apply to: (a) initial reviews, (b) continuing reviews, (c) modifications (amendments), (d) unanticipated problem reports; and e) protocol deviations.

Members also review and vote on other pertinent business, including compliance oversight activities, which the Chair includes on the agenda.

Experienced members may be appointed by the Chair to review research activities that qualify for expedited review or activities that may be considered exempt.

d. Attendance Requirements

Members are provided with notice of meeting dates several months in advance and are expected to regularly attend meetings of the IRB to which they are appointed. Members are expected to notify IRB staff affiliated with their respective IRB sufficiently in advance of known absences for the staff to substitute registered alternates, at the discretion of the Chair and Manager, whenever possible; this is a requirement if the absence will affect quorum. When a situation arises that will result in an unanticipated absence, the member is expected to notify the staff at the earliest opportunity.

At the discretion of the Chair and in consultation with the relevant IO designated on the applicable FWA, three consecutive absences by a member or a pattern of absences that affects the functioning of the Board may result in removal.

e. Removal, Resignation

Prior to the start of each fiscal year, the Chair of each IRB, in consultation with the ED, AD, respective Vice Chair(s), and/or respective IRB Manager, may determine that the appointment of any regular or alternate member whose term is expiring should not be renewed.

Members may be removed in mid-term by the IO designated on the applicable FWA, or the EVPR. Recommendations for removal by the Board Chairs, other members of the Board, investigators, or other university officials will be considered.

Resigning members must notify the Board Chair and/or the ED of their intentions in writing. The ED will notify the appropriate IO.

Individual termination letters are prepared and signed by either the ED, or an IO. Once signed, copies are distributed to appropriate individuals, including the IO, respective IRB Chair, ED, AD, and Manager of the relevant IRB. A copy is retained in the IRB member file.

f. Liability Coverage for IRB Members

IRB members are protected from personal liability under the Columbia insurance policy, which protects individuals serving on all University committees.

g. Education and Training

Members are expected to participate in initial and continuing education initiatives to understand, and keep abreast of, changes to institutional policy, relevant legal statutes, the RASCAL system, and evolving interpretation of regulations, policies, and laws. Details of education and training initiatives are provided in Section X of these written procedures.

h. Confidentiality/Conflict of Interest

All Board Members are required to sign a Confidentiality/Conflict of Interest Statement (Working Practice Document #76), the concepts of which, in regards to COI, are reinforced during the orientation session for new members. The statement also articulates the need and expectation for Board deliberations and details of the protocols that are submitted to the IRB to remain confidential.

IRB members should not disclose the results of IRB reviews to investigators or others without the expressed permission of the IRB Chair, IRB Manager, or the ED.

Board members who have a conflict of interest with a particular protocol, event, or issue that is reviewed by the Board are expected to recuse themselves from relevant Board deliberations and votes.

1) For convened meetings, this means that the Board member must leave the room during the Board discussion and vote; the conflicted member will not count towards quorum for that review. The Board may ask the conflicted member questions related to the protocol prior to completion of the discussion. IRB staff, during preparation of the agenda for full Board meetings, will identify those submissions for which a Board member who is expected to be in attendance for the meeting has a conflict; this helps to ensure compliance with the need for any such members to leave the room during discussion of the protocol for which a conflict exists.

2) In the case of expedited reviews, a Board member who has a conflict of interest in relation to a specific protocol is expected to notify the Chair if a submission for that

protocol is assigned to the member for review. IRB staff who conduct the administrative review and identify a conflict will include that information in the Notes for the protocol.

3) For both full Board reviews and expedited reviews, the RASCAL system will not allow an individual who is named among study Personnel on a submission to be assigned as a reviewer for that submission.

4) Whenever possible, IRB staff will not assign a protocol, for which an IRB member is the PI, to the IRB on which the PI is a member.

Conflict of Interest parameters, including definitions of "financial interest" and "family member", may be found in the University Policy on Financial Conflicts of Interest and Research (Working Practice Document 219 and posted online at: http://evpr.columbia.edu/files_sponsoredprojectprocedures/imce_shared/COI_Policy_4_3_09_new.pdf).

Primary reviewers are assigned by the Chair based on expertise and availability. There is no selection of IRB members as primary reviewers by investigators.

3. IRB Administrative Staff

a. Support

The IRB Administrative Office provides sufficient professional and administrative support, and adequate resources, to ensure compliance with federal and state regulations and institutional policies for the protection of human subjects in research. The commitment of staff for the IRB is evaluated internally by the AD, in conjunction with the IRB Managers and ED, on a continual basis and additional support is provided as needed. Through regular meetings with the VPRO and CUMC IO, the ED and AD communicate office-wide requests for additional support as needed.

Adequate meeting and office space are provided for the IRB and staff. Office equipment and supplies, including file cabinets, computers with Internet access, and copy machines, are available to the IRB and staff.

b. Duties

Staff members are categorized as either officers or support staff. Duties for all staff are described in the job description for the specific position held by each individual (Working Practice Document #91).

To improve quality, performance and efficiency, periodic performance evaluations are conducted for officer-level staff, while regular feedback is provided to support level staff. The current Supporting Staff Association (SSA) and 2110 UAW (i.e., unions for support-level staff at

CUMC and CU, respectively) Collective Bargaining Agreements with the University guide the supervision and employment of support staff.

c. Education and Training

The IRB Staff will complete the same core educational program that is provided to Board members during their orientation sessions. This includes training on the regulations and the Columbia IRB policies and procedures. The IRB staff will also be provided ongoing and continuing educational opportunities (IRB seminars and workshops; distribution of continuing education information; and access to the IRB website and library). Details of education and training initiatives are provided in Section X of these written procedures.

V. Procedures for Processing of Submissions to the IRB

This section describes the type of information and documentation that must be submitted to the IRB for the review of different events (e.g., new protocol, modification, unanticipated problem report, renewal) and varying types of research (e.g., drug study, international trial, collaborative project). In addition, particular information required when vulnerable populations are involved is also explained.

Each variable is described individually and is provided as guidance for use in the preparation of a submission. Therefore, for example, if a submission is for a new protocol that involves an investigational drug administered to children, the information described in each of the relevant sections (i.e., new protocol, drug study, and minors) should be reviewed and the relevant materials included in the submission.

A. Preparation of Submissions

Researchers create protocols electronically in the University's web-based protocol tracking system, RASCAL. Various options exist for incorporation of pertinent information about the research proposal, to accommodate the various types of documentation available to the researcher. Information may be entered in fields that appear in the submission on a composite Data Sheet, existing documents may be attached electronically, and there is also a feature that permits construction of consent documents, called the "Consent Form Builder", within RASCAL. Relevant documents that are available to the researcher only in paper form may be scanned and attached.

Step by step instructions for creating a protocol and consent document within RASCAL may be found in Working Practice Documents #64 and #71 (Creating a RASCAL Protocol, and RASCAL Consent Form How-To), respectively. In addition, a comprehensive manual for submitting events to the IRB for review, entitled "User's Guide to the RASCAL IRB Module", is posted on the IRB websites: http://www.cumc.columbia.edu/dept/irb/ and http://www.columbia.edu/cu/irb/.

RASCAL accommodates the various events that may occur during the active life of a protocol, i.e., initial proposal, modification, unanticipated problem, protocol deviation (submitted as modification or unanticipated problem report, as appropriate), renewal, and termination. Emergency Use follow-up reports may also be submitted and processed in RASCAL.

Information and material entered for new events is accessible only to personnel listed on the protocol while the protocol status is "creating", i.e., prior to initial submission to the IRB.

All actions related to a specific event, including material submitted, information entered, correspondence generated, internal IRB notes and documents, history and status, are stored together electronically as "events" (per RASCAL terminology) within the RASCAL "file" for each overall project. IRB staff and members may view all entries and attachments for a given event, once the event has been submitted, and may attach documents to the submission, but may

not otherwise modify the submitted material. Attachments by staff and members are clearly labeled with the name of the individual who attached the document, and the date they are attached. If the IRB modifies an attached document (to decrease returns by making changes which involve standard text), when the revised document is reattached, it will be documented by the RASCAL system that IRB staff attached it. In such instances, IRB correspondence will explain that the document has been revised, and advise the study team that they should immediately advise the IRB if the changes are not acceptable.

The researcher has access to all elements of the protocol except the internal IRB notes and documents, reviewer identification, minutes, and correspondence transmitted between IRB staff and/or between IRB members and staff.

IRB review is based on the material submitted electronically by the researchers via RASCAL. Literature reviews by members and notes entered to document conversations with members of the research team may also be considered during the review.

Annual conflict of interest statements and evidence of satisfactory completion of training for research personnel in GCP (or Protection of Human Subjects in Research, as applicable), Handling Biohazard Materials, and HIPAA, are documented electronically in accordance with RASCAL procedures and reflected on the Data Sheet of the submission. Documentation regarding completion of the Research with Minors module, within the online CITI program, is maintained within RASCAL and appears on the RASCAL Data Sheet.

An electronic protocol-specific conflict of interest statement is also required for the PI, all co-investigators, study coordinators, and regulatory coordinators as part of the submission approval process.

B. Documents/Information Needed for Each Type of Event

1. Submission materials: New protocol

General Information (Working Practice Document #35), Personnel, Subjects, Funding, and Location screens (found within Working Practice Document #70, "User's Guide to the RASCAL IRB Module") collect the data that will constitute the basic application for review.

The following information or documentation should be included or attached for basic submissions:

a. list of personnel (members of the Columbia research team) involved in the research, with certification of any required education/ training;

b. research objectives and hypothesis, as applicable;

c. description of the anticipated study population, including demographic information regarding anticipated age, ethnicity, and gender;

d. consent documents (e.g., consent form, parental permission form, assent form, information sheet, oral script) and description of the consent process, or request for waiver of consent and/or written documentation of informed consent, with justification for the waiver(s);

e. funding information and, for supported projects, the grant, contract (if available), or other documentation of the supported research, e.g., sponsor's protocol, investigator's brochure;

f. approvals from other institutions, if applicable and available;

g. study instruments, if applicable (e.g., survey, focus group guide, interview script);

h. recruitment material, if applicable (e.g., recruitment flyer or letter, letter to clinicians, text for Internet advertisement);

i. any other material pertinent to assessment of the potential risks and benefits of the proposed research, e.g., mechanisms incorporated to minimize risk;

j. completion of the Human Specimens section if any tissue or fluid will be obtained from subjects or stored specimens will be used;

k. justification for exemption, if applicable;

l. plans for maintaining privacy of participants and confidentiality of data, as applicable;

m. data and safety monitoring plan, as appropriate to level of risk presented by study procedures;

n. completion of the Investigational Products section if a drug, device, or biologic is under investigation as part of the research.

Additional information and/or documentation may be required for specific types of research (e.g., drug studies, research with pregnant women). Details are in the applicable segment presented later in this section (Section V).

2. Submission materials: Modification

Any proposed change or modification to the protocol that was approved by the IRB must first receive prospective IRB approval, unless such a change is necessary to eliminate or minimize an imminent harm to subjects.

If the protocol was eligible for expedited review, and the proposed change(s) are not such that the protocol would no longer be eligible for expedited review, then the modification may also be reviewed under an expedited review process.

If the overall protocol requires review by the convened IRB, and the change is non-substantive in nature, then the IRB may approve such a change by expedited review. Full Board review of the modification is required if the proposed change(s) are substantive in nature (e.g., increase risk, add a treatment arm, expand the study population to include vulnerable subjects).

If it is discovered that there is an imminent harm to subjects, the investigator should implement any change(s) necessary to reduce or remove such harm and subsequently submit a modification to the IRB so that such change(s) are approved by the IRB for all subsequent research activities under the protocol. Changes made without prospective IRB approval, to address an imminent harm to subjects, are considered deviations, which are explained in more detail in Section V.B.6, below.

Any change in the protocol that is necessary for the enrollment of a specific subject (i.e., deviation from the approved inclusion/exclusion criteria) also needs prospective IRB approval. If a subject who does not meet the enrollment criteria is enrolled, even if the sponsor has agreed to such enrollment, this would be considered a protocol deviation (if the study team identified the change before enrollment) or violation (if the study team did not identify the change before enrollment) by the IRB. Protocol deviations and violations that occur during the study should also be submitted as modifications, unless the deviation involves an unanticipated problem involving risks to subjects; the latter should be submitted using the unanticipated problem reporting module. See Section V.B.6 for additional information regarding submission of reports of deviations and violations.

The Modification Information Form (Working Practice Document #69) must be completed in RASCAL when changes to the approved protocol are requested. This form solicits the following information:

a. summary of and explanation for the requested modification or addendum to the approved protocol;
b. number of subjects currently enrolled;
c. study enrollment status, e.g., enrollment ongoing, study closed to enrollment.

The following information or documentation must be attached or included:

a. clean and highlighted copies of revised documents, or a clean copy with a clear explanation of what has changed, if documents have been revised;
b. supporting documentation of modification from the sponsor, if applicable;
c. updated personnel list, if personnel change is involved;
d. updated Study Description, if previously submitted information has changed;
e. plans to obtain updated consent from enrolled subjects if new information that may affect their willingness to continue participation is involved, or justification for not obtaining updated consent when new information is available.

3. Submission materials: Renewal (Continuing Review)

Notification that continuing review is required will be sent automatically by the RASCAL system to investigators at 90, 60, and 30 days prior to the expiration date of the current IRB

approval. Investigators are required to submit renewal requests in RASCAL and are encouraged to submit appropriate reports for ongoing research activities 60 days prior to the expiration date of the IRB approval for the study.

The Renewal Information Form (Working Practice Document #61) must be completed in RASCAL. This form solicits the following information:

a. study enrollment status, (e.g., enrollment ongoing, study closed to enrollment);
b. date enrollment began at CU site;
c. whether a Certificate of Confidentiality (COC) is required;
d. if a COC exists, the date it expires;
e. summary of any relevant recent literature or interim findings;
f. explanation for any change including a change to risk/benefit ratio;
g. list of papers pending or published about this study;
h. synopsis of the results to date.

In addition to completing the Renewal Information form, the Subjects section in RASCAL must be updated to reflect, at a minimum:

a. original number of participants anticipated;
b. number of participants enrolled to date at CU site;
c. number of participants enrolled last year at CU site;
d. number of participants who completed the study at CU site;
e. number of participants expected to enroll next year;
f. number of, and explanation for, participant complaints at CU site;
g. number of, and explanation for, participants removed by physician;
h. number of, and explanation for, participants who withdrew from the study;
i. number of participants enrolled to date at other sites;
j. demographic information for subjects enrolled at CU site;
k. if enrollment is less than anticipated, the reasons for, and strategies to remedy, this situation;
l. subject population justification;
m. subject compensation and justification, if applicable;
n. consent waiver or alteration requests, if applicable;
o. recruitment URL, if applicable.

The following information or documentation must be attached:

a. summary of all Unanticipated Problems that occurred during the review period and since the beginning of the study; details of the elements that should be included in the summary are articulated in the Columbia Reporting to the IRB of Unanticipated Problems Policy (Working Practice Document #02), as are options for submitting a monitoring entity report in lieu of the summary;
b. recent Data Safety Monitoring Board (DSMB) or other relevant multi-center trial reports, if applicable;
c. for studies that are open to enrollment, a copy of the current informed consent document(s), and any newly proposed revisions to the consent document(s);
d. documentation to support changes to the protocol, consent document(s), study instrument(s), or other study-related material, if a modification is submitted with the renewal;
e. any withdrawal of subjects from the research or complaints about the research since the last IRB review;
f. any other relevant information, especially information about change in risks associated with the research, notifications to research participants of new findings which may affect their willingness to continue participation, and continuing protection under a Certificate of Confidentiality, if applicable.

For federally funded, multiple year projects, a copy of the most recent Progress Report should be included. For all sponsored projects, if changes in the terms or type of funding have occurred, the Funding section should be updated and the appropriate documentation attached.

4. Submission materials: Report of unanticipated problems involving risks to subjects or others

The Unanticipated Problem (UP) Report (Working Practice Document #188) in RASCAL must be completed to report incidents, experiences, and outcomes (including adverse events) in accordance with the CU Reporting to the IRB of Unanticipated Problems Policy (Working Practice Document #02). This form collects information pertinent to the incident, experience, or outcome being reported, including the following:

a. subject identifier and incident, experience, or outcome keyword;
b. date, location, and description of the incident, experience, or outcome;
c. relationship of the incident, experience, or outcome event to the study;
d. evaluation of whether the incident, experience, or outcome was unanticipated, related to participation in the study, and suggests an increase in risk to subjects or others;
e. date and means by which the PI became aware of the incident, experience, or outcome;
f. entities to which the incident, experience, or outcome was reported;

g. evaluation of whether changes are required to the protocol and/or consent document(s).

Supporting documentation may be attached electronically to the Report. If changes to the consent form or protocol are required, a modification must be submitted as a separate event in RASCAL.

Protocol deviations that result in unanticipated problems involving risks to subjects should be submitted via the Unanticipated Problems Report module.

Reports of Unanticipated Problems for protocols reviewed in accordance with the terms of an IRB Authorization Agreement, when Columbia is not the IRB of Record, should be submitted to the IRB designated in Working Practice Document #118, "Processes for Review and Monitoring of Protocols Subject to IRB Authorization Agreements".

5. Submission materials: Termination

A Termination Report form (Working Practice Document #67) must be submitted when all study procedures are completed, including analysis of identifiable data collected from the study, and IRB oversight of the project is no longer required. For multicenter studies, termination is appropriate: a) when all study procedures are completed at CU, if CU is not the lead institution with responsibility for other sites; or b) when all study procedures are completed at all sites, if CU is the lead institution with responsibility for other sites.

The Termination Report form solicits varying details depending on the type of review performed by the IRB (e.g., expedited review, full Board review). Studies that were last reviewed by a full Board process will require the following information:

a. changes or amendments since the most recent approval (including changes in personnel since the most recent approval and additional information about risk associated with this study);
b. total number of participants in the study;
c. number of participants since the most recent approval;
d. number of participants who withdrew from the study;
e. number of participants who complained about the study;
f. summary of any recent literature or findings;
g. brief summary of results.

The Termination Pre-Review and Return Criteria document (Working Practice Document #111) guides IRB staff on the pre-review of terminations. Staff document their pre-reviews in the Notes section of RASCAL.

6. Submission materials: Report of Protocol Deviation or Violation

All protocol deviations, violations, and instances of noncompliance with Columbia policies or IRB determinations must be reported to the IRB. A protocol deviation is defined as a change in the protocol for one or more subjects that is identified by the research team before the change is implemented and should be approved by the IRB before implementation. A protocol violation is defined as a protocol change or modification that was not approved by the IRB and is identified by the research staff after the change was implemented. Protocol violations may be considered as non-compliance with the federal regulations for the protection of human subjects.

The IRB recognizes that some deviations regarding inclusion/exclusion criteria are identified shortly before the subject is scheduled for randomization or entry into the study and that a quick review by the IRB is important for the study. For funded studies, the sponsor's concurrence that the individual may be enrolled should be provided with the submission. In time-sensitive situations, the investigator should follow his/her submission to the IRB with an e-mail outside of RASCAL to the Manager of the IRB that approved the study.

If the Protocol Deviation/Violation is unanticipated and involves risks to subjects or others, it should be submitted to the IRB within one week (5 business days) as an Unanticipated Problem Report in RASCAL.

Protocol Deviations/Violations that do not involve risks to subjects or others should be submitted promptly as a Modification in RASCAL.

The description of the circumstances surrounding the deviation/modification should be clearly stated in the Unanticipated Problem Report (Working Practice Document #188) or in the summary section of the Modification Information form (Working Practice Document #69), as applicable.

The following information should be included:

a. complete description of the deviation/violation;
b. explanation of why the deviation is necessary, or why the violation occurred;
c. whether the deviation affected, or the violation affects, the risk/benefit ratio for subjects, integrity of the research data, and subjects' willingness to continue study participation; and
d. for protocol violations, a description of the corrective measures that will be taken to prevent a recurrence of the same or similar violations.

Supporting documentation may be attached electronically, and should be provided whenever available or pertinent.

7. Submission materials: Emergency Use Report

FDA regulations permit use of an investigational drug or device, without IRB approval, in very limited circumstances. Such use is considered to be an emergency clinical use, and FDA requirements for the research use of an investigational agent do not apply. The involvement of the IRB prior to the administration of the agent is to serve as a facilitator for shipment of the investigational product and initiation of a monitoring process. The FDA must be notified of all emergency use situations by the manufacturer or sponsor.

Only emergency life-threatening situations that will be treated with an investigational agent, for which an approved protocol is not available, in an effort to save a patient's life or loss of a part of the body (e.g., eye, limb) are to be considered for the emergency use exemption. None of these situations will be considered research and therefore data collection for research purposes is not permitted. Physicians are encouraged to contact the IRB office immediately if such a situation arises.

Consent options for emergency use situations are defined below; proposed procedures must be described in the emergency use request to the IRB prior to the emergency use:

a. If the consent form is prepared at the time of submission of the emergency use request, it should be attached and submitted with the EU request;

b. If consent will be obtained, but the form is not yet available, this should be so stated, and a copy of the form submitted with the a follow-up report within 5 days of the use of the test article;

c. If waiver of consent is requested, documentation that the criteria for waiver codified at 21 CFR 50.24 have been met must be included.

In addition, CU policy requires documentation to be provided that the patient's condition is life- and there is no effective alternative treatment available. Concurrence by a physician who is not otherwise involved in the use of the investigational product is also required by Columbia policy regardless if consent was obtained. If this certification is not available at the time of the request for emergency use, it must be provided in a follow-up report within 5 days of the use of the test article.

An Emergency Use (EU) report must be submitted to the IRB when an investigational product has been administered in accordance with the emergency use provisions identified in 21 CFR 56.104(c) and 21 CFR 50.23, if all required information was not provided with the emergency use request. The following information should be included:

a. product name and type (i.e., drug, device, biologic);

b. if a device, product model/version number, if applicable;

c. IND or IDE number, if one has been obtained for this use;

d. description of product;

e. name, affiliation of non-participating physician and date of affirmation;

f. number and submission date of protocol submitted for IRB review of this article, if applicable;

g. date of notification to FDA.

Hard copy submissions should include the same information.

C. Material Needed for Review of Particular Types of Research

1. Submission materials: Drug research

Research that involves a drug or drugs may vary in design, from investigation of the safety and/or efficacy of investigational agents, to comparison of two approved agents, to the evaluation of approved drugs for indications other than those for which they were approved.

A drug is defined in the revised federal Food, Drug and Cosmetic Act as:

a. articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and

b. articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

c. articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

d. articles intended for use as a component of any articles specified in clause a, b, or c; but does not include devices or their components, parts, or accessories.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material and/or information is required for all research involving drugs:

a. sponsor protocol, if industry-sponsored;

b. Investigator's Drug Brochure (IDB), if industry-sponsored;

c. package insert, if approved drugs are administered;

d. documentation of current FDA status, if an Investigational New Drug (IND) exemption is indicated;

e. completion of the Investigational Products section (Working Practice Document #92) for each agent involved.

When drugs that are not yet FDA-approved will be used for research purposes, plans for handling of the investigational agent should be included in the submission to the IRB. These should be in accordance with the CUMC Research Pharmacy procedures and NYP policy P168,

Investigational Drugs: Use and Control; a statement that the relevant policy(ies) will be followed is sufficient for the IRB submission.

2. Submission materials: Research with Biologics

Protocols that involve research with biologics require similar submission materials and are reviewed similarly to research with investigational drugs.

A biologic is defined as any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or analogous product, or arsphenamine or its derivatives, applicable to the prevention, treatment or care of diseases or injuries of man.

Review and approval by the Institutional Biosafety Committee (IBC) is required for biologics that involve recombinant DNA. When gene transfer is involved, documentation of a decision by the NIH Recombinant Advisory Council (RAC), when their review is required, is expected.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material and/or information is required for all research involving drugs:

a. sponsor protocol, if industry-sponsored;
b. IDB, if industry-sponsored;
c. package insert, if approved drugs are administered;
d. documentation of current FDA status, if an IND for a biologic (BB-IND) is indicated;
e. completion of the Investigational Products section (Working Practice Document #92) for each agent involved.

3. Submission materials: Device research

Research that involves a medical device may vary in design, from investigation of the safety, efficacy and practicality of investigational devices, to comparison of two approved devices, to the evaluation of approved devices for indications other than those for which they were approved.

A medical device is defined in the revised federal Food, Drug and Cosmetic Act as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

a. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
b. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

c. intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material and/or information is required for all research involving devices:

a. device manual, if industry-sponsored;

b. documentation of current FDA status, (e.g., FDA approval letter with terms if an Investigational Device Exemption (IDE) is indicated, printout of approved indications from FDA website if 510(k) approval);

c. d. completion of the Investigational Products section (Working Practice Document #92) for each agent involved.

A sponsor's determination of non-significant or significant risk, and basis for the determination, is recommended for studies that do not already have an approved IDE. If this information is not provided, the IRB will make its determination absent this input; if additional information is needed, the determination, and hence the overall review, may be delayed. Alternatively, the result may be a decision that is inconsistent with the sponsor's but would nevertheless be binding absent justification for a reconsideration from the sponsor.

When devices that are not yet FDA-approved will be used, plans for handling of the investigational article should be included in the submission to the IRB. The following factors should be addressed:

a. When recruitment and ordering of devices will begin (e.g., that no patients will be contacted or recruited, and no investigational devices will be ordered, until IRB approval has been obtained and applicable contracts have been signed);
b. That the PI is responsible for ordering, and proper accountability, handling, and storage, of devices;
    1) How and by whom devices will be ordered (e.g., ordering will be done in accordance with the terms of the protocol and contract, and only after IRB approval is obtained);
    2) By whom devices will be received (e.g., devices will be received only by the PI or designee, or NYP personnel when there is an NYPH policy or procedure for device management (e.g., in Operating Room));
    3) How device accountability will be documented including receipt from manufacturer, method for labeling and tracking individual devices date of use, subject identifier, and lot number of the device, and return of (or destruction of in accordance with manufacturer's instructions/protocol) unused devices to the manufacture or sponsor. The spreadsheet or dispensing log for device accountability should be included with the plan for handling investigational devices);

4) By whom devices may be handled (e.g., devices will be handled only by individuals listed on the protocol or by NYP personnel when there is an NYP policy or procedure in place (e.g., in Operating Room));
5) Who will ensure the sterility of the device prior to use with a subject (i.e., either the product is shipped to the PI in sterile condition or the device will be sterilized on the premises per the protocol and NYP policies).
6) In what manner will devices be stored to ensure accountability, sterility, and integrity of packaging (e.g., a plan for storing devices securely to ensure physical stability of packaging and appropriate temperature, and separate from similar commercial and/or investigational devices will be implemented);
7) Procedures by which disposition of devices will occur (e.g., devices will not be destroyed, devices will be disposed of in accordance with the manufacturer's or sponsor's (as applicable) requirements (e.g., returned to sponsor)).
8) If the device will be explanted from the subject, plans to first send the device to Pathology for their review in accordance with standard practice.

c. That manufacturer and/or sponsor representatives who are involved with use of the device at a study site under the direction of a Columbia investigator will abide by site requirements and policies regarding privileges and access to facilities, patients, and confidential information.

4. Submission materials: Emergency research

Emergency research refers to the study of acute, life threatening clinical situations. Often, informed consent from the subjects is not feasible because the subject lacks the capacity to provide their own consent (e.g., unconscious) and/or there is insufficient time because treatment must be promptly administered. The conduct of planned research in life-threatening emergent situations requires special consideration by the IRB, including consideration of whether consent may be waived. The specific conditions under which prospective consent of the subject may be waived are provided by 21 CFR 50.24.

If waiver of consent is proposed for those subjects who are not capable of providing consent, and do not have a legally authorized surrogate present, the research plan must include not only public disclosure of the study to the community in which the research will be conducted, but also community consultation. The purpose of the community consultation is to assess whether members of the local population at large would approve of the conduct of the emergency research, i.e., whether they are in favor of such procedures performed on them if they were in a particular emergency situation. The community consultation should include individuals that represent the targeted subject population that will be enrolled in the study. The community consultation must be completed before IRB approval. It is recommended that the research team meet with the IRB staff to discuss the plan for community consultation prior to its initiation.

The plan for the emergency research study, including the plan for community consultation and public disclosure, must also be approved in advance by FDA if the research involves an investigational or FDA-approved product. If the emergency research study is federally-

supported or conducted and does not involve an investigational or FDA-approved product, approval must be obtained from OHRP (on behalf of the DHHS Secretary). The plan must be submitted to the FDA under an emergency IND/IDE by the sponsor or PI responsible for the IND/IDE. The community consultation and the public disclosures, however, generally do not have to be completed prior to submission for FDA approval. Therefore, the appropriate sequence of events would generally be: a) consultation with the IRB; b) community consultation; c) IRB approval; and d) FDA approval.

The IRB may approve the study prior to FDA approval of the IND/IDE. When this occurs, the IRB approval will specifically restrict enrollment of subjects as appropriate until the IRB receives notice of FDA approval of the IND, and all outstanding concerns have been adequately addressed.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material and/or information is required for all research involving emergency research:

a. justification for conducting the research in the proposed context, including enough information for the IRB to make all determinations required in Section VI.D.10;
b. detailed process for obtaining consent for subjects who are able to consent;
c. for those subjects who are not able to provide informed consent, a description of family notification of research participation, when possible, and providing the opportunity for the family to object to participation; and plans for informing the patient of participation if/when the patient regains cognitive capacity;
d. procedures for determining who is a legally authorized representative, when permission will be sought from someone other than the parent of a minor child;
e. description of the efforts by which the community has been advised of the planned emergency research.

At the time of continuing review, unless required sooner by the IRB, the investigator will need to summarize efforts made to contact family members of those subjects who were not able to provide their own consent.

5. Submission materials: Research involving pregnant woman and fetuses

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material is required for all research involving pregnant women, fetuses, and neonates:

a. information to support the findings required by Subpart B of 45 CFR 46 for participation of pregnant women and fetuses in research;
b. description of the additional precautions that will be taken to ensure that legally effective informed consent is obtained, when women in labor will be enrolled. Institutional guidance

(Working Practice Document #10) on when it may be acceptable to approach women in labor for purposes of research participation should be considered when developing this information.

6. Submission materials: Research involving prisoners

In addition to the material listed in the preceding section related to the type of event (e.g., new protocol, renewal, modification), the following material is required for all research involving prisoners:

a. information to support the findings required by Subpart C of 45 CFR 46 for participation of prisoners in research;

b. rationale for including prisoners in the research, or limiting research participation to prisoners.

7. Submission materials: Research involving children

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material is required for all research involving children, i.e., information to support the findings required by Subpart D of 45 CFR 46:

a. description of procedures used to obtain assent, or justification for not obtaining assent;

b. when assent will be obtained, identification of the ages for which assent will be required, and a description of the method used to document that assent was provided, e.g., written documentation on an assent form, verbal agreement documented by researcher in the research record;

c. description of procedures for obtaining, and forms used to document, parental permission;

d. investigator's initial assessment of risk level and potential for benefit to subjects or others;

e. sufficient information for the IRB to determine the level of risk, and whether there is the prospect of direct benefit to the individual subject;

f. statement regarding the inclusion of wards if the research involves greater than minimal risk without the possibility of direct benefit, i.e., whether wards will be included and if so, what procedures have been developed for identifying an advocate for each ward;

g. procedures for determining who is a legally authorized representative, when permission will be sought from someone other than the parent of a minor child.

The Child Involvement section in RASCAL, which solicits the information described above, must be completed by the investigator if he/she has indicated that children will be involved in the study. This section is designed to present to the investigator the questions for which information is required, depending upon the level of risk and prospect of benefit to subjects.

Researchers who anticipate that children will be included among their study subjects are advised to review the Columbia policy, Research Involving Children (Working Practice Document #107), which articulates the institution's expectations for parental permission, assent, risk/benefit analysis, and related issues. The policy is posted on the CUMC and CU-MS IRB websites.

8. Submission materials: Research involving other vulnerable adults

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material is required for all research involving vulnerable populations:

a. description of procedures incorporated into the protocol to ensure that the rights and welfare of individuals with decreased autonomy will be protected;

b. description of procedures that will be utilized to obtain legally effective consent;

c. where applicable, description of procedures that will be utilized to determine competency to provide consent initially or during the course of participation, the latter for studies in which it is expected that cognitive capacity may become diminished;

d. procedures for determining who is a legally authorized representative or appropriate health care proxy, when one is needed to provide consent;

e. description of procedures that will be utilized to minimize risks related to the vulnerability of the prospective subjects;

f. description of procedures that will be in place to eliminate elements of undue influence or coercion.

9. Submission materials: Research involving non-English speaking individuals

If the inclusion of non-English speaking individuals is anticipated, the consent document(s) must generally be translated by an acceptable translator, as defined in the CU IRB Enrollment of Non-English Speaking Subjects in Research Policy, into the prospective subjects' first language or language of choice. Certification of the translation, as described in the Policy, must be provided. It is not sufficient in most cases to rely on verbal translation of English consent documents during the consent process.

If a non-English speaking individual is unexpectedly encountered who otherwise meets eligibility criteria, and the trial involves an intervention that offers the prospect of direct benefit, the short form consent process may be used and use of the process must be documented. The summary document (in English) and the participant's attestation (in his/her first language or language of choice) must be approved by the IRB. Efforts to translate the entire approved English consent document are encouraged, whenever possible.

See Working Practice Document #101, Enrollment of Non-English Speaking Subjects in Research Policy, for details on translation options.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material and description of procedures are required for all research in which the involvement of non-English speaking subjects is anticipated:

a. description of procedures to obtain consent in the subject's language of choice;
b. statement that consent and recruitment documents will be translated after the English version is approved (if this is not included in the submission, the IRB approval letter and correspondence will articulate the need for translation);
c. after the English version is approved, submission of translated documents as a modification, with certification of exact translation.

At the time of continuing review, if previously approved consent and recruitment documents have not changed, the same translation may be submitted for review.

10. Submission materials: Research involving students or employees as subjects

Ethical concerns may arise if a study recruits individuals in positions subordinate to the PI. At times, however, recruitment of individuals in this situation may be necessary to accomplish study objectives. In those cases, the investigator must justify the use of this population and identify how elements of coercion or undue influence will be addressed. The Board will consider whether proposed procedures to minimize such elements are adequate, and request revisions or additions if necessary.

These measures are not, in general, intended to apply to research conditions under which subjects are recruited by flyers or other advertisements posted publicly to which individuals subordinate to the investigator may elect to apply. There may, however, be instances in which the IRB must consider whether enrollment of subordinates is not appropriate, even if recruitment is via flyer and initiative by the prospective participant is required, e.g., when there is the potential that the student/employee may feel that they must participate in order to be seen as favorable or cooperative to their instructor/employer.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material is required for all research involving students or other individuals in a subordinate position to the researcher.

a. justification for use of this population;
b. description of procedures that will be utilized to avoid elements of coercion or undue influence;
c. explanation of other options for obtaining course credit if research participation offers such incentives;
d. explicit instructions for advising subjects of the voluntary nature of participation.

When students will be recruited, the "Students as Research Subjects" guidance (Working Practice Document #128) should also be reviewed for applicability.

11. Submission materials: International research

IRB review of international research raises additional considerations related to obtaining local knowledge of applicable laws, institutional commitments and regulations, standards of professional conduct and practice, cultural norms, and local community attitudes. Physical, social and psychological risks may vary from those in the New York City communities within which the Columbia campuses reside, i.e., the area "local to" the CUMC and CU-MS IRBs. Assessing the risks and benefits of research conducted internationally may raise challenges if there is not adequate knowledge of the local setting. Care must be taken to ensure that the cultural norms of the host country are respected and that the participants will not suffer adverse consequences from participation, such as being subjected to retaliation from local authorities or the local community.

To that end, evaluation of the protocol by a review board local to the study site, consultation with an expert in the respective country, and/or other means to obtain knowledge of the local context is required.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material or considerations are required prior to approval by the IRB.

a. documentation of knowledge of local context, e.g., details of the local context to provide a basis for the IRB review;
b. local IRB/ethics committee approval, evaluation by consultant, or input from an individual or entity with adequate knowledge of the study site (if this documentation is already available at the time of the CU IRB submission);
c. agreement that consent documents will be translated after the English version is approved, if the study population is expected to include non-English speaking individuals;
d. identification of local individuals, if any, who will participate in conducting the research, and a description of their roles;
e. where appropriate, letter(s) authorizing conduct of the study at the international institution or organization.

If sufficient information about the proposed research site, to satisfy the IRB's requirement for knowledge of the local context, is not provided in the submission, such will be requested as a result of the administrative pre-review. Information about the local context is required for all international studies, and may be provided via formal consultant review, input from a knowledgeable individual, or review by a local IRB or ethics committee.

In general, if local ethics committee approval is required, it should be obtained after review by the CU IRB. If local ethics committee review is conducted before the CU IRB review, the approved consent document(s), explanation of issues raised by the local committee during its review, if available, and approval letter from the local committee, should be considered in the CU IRB review.

If CU IRB review occurs before the local ethics committee review, CU approval to commence study procedures would be contingent upon receipt of the approval by the local ethics committee, which should employ standards that are appropriate for Columbia's HRPP.

12. Submission materials: Substudies

Substudies may be defined as projects that are developed to answer a research question that has arisen as a result of an ongoing study, i.e., there is a logical evolution or expansion of the initial research hypothesis.

The determination of whether a substudy should be submitted as a separate, new RASCAL submission, or as a modification to an approved protocol, is dependent on the relationship of the new procedures to the existing protocol, e.g., objectives, subject population, consent procedures, study instruments, risk and benefit. In general, if the population, consent procedures, and objectives vary significantly from the approved study, such that the IRB can no longer make one set of required determinations for the entire RASCAL protocol, the substudy should be submitted separately. In such cases, the approved main study should be referenced in the new submission so that, where feasible, both can be reviewed by the same IRB and primary reviewers.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material is required for all substudies:

a. an explanation of the relationship between a previously approved protocol and the substudy that is being submitted for review;
b. a description of the modifications, if any, that will be made and submitted to the IRB for review, to recruit from the main study, if applicable;
c. if subjects from the main study will be recruited for the substudy, a description of how the substudy will be introduced to the subjects;
d. details of data use and sharing, if applicable, between studies.

13. Submission materials: Collaborative research not conducted under an IRB Authorization Agreement

Researchers affiliated with Columbia may collaborate with individuals from other institutions on a specific research project involving human subjects. When this occurs, the IRB needs to know enough about the activities at each site to be able to accurately determine the risks and benefits

of the activities for which CU has oversight, and the documentation, if any, required from each site.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material/information is required for all collaborative research:

a. For all collaborative projects:
    1) the name and title of, and contact information for, the individual (identified by role) who is responsible for the conduct of the project at the collaborative site(s);
    2) the procedures that will be conducted at each site (level of detail will be dependent upon CU role, i.e., whether CU is the lead institution, one of the study sites, coordinating center, etc.);
    3) the funding mechanisms involved;
    4) identification of the individual and institution who will serve as the overall PI for the project;
    5) clear description of what the CU personnel will be doing and what will be done, in relation to the research study, at CU;
    6) appropriate authorization for research at the site, and IRB approval, as applicable;
    7) plans to enter into, or attachment of an executed, IRB Authorization Agreement if one or more collaborating institutions will rely on the IRB at another of the collaborating institutions.

b. In addition, if CU is the lead institution:
    1) the status of IRB approval at each site or arrangements previously made or in progress to delegate authority for review;
    2) description of services provided by coordinating centers, and identification of the coordinating centers, if applicable;
    3) a written plan explaining how regulatory compliance will be ensured for each site engaged in the research. The plan should include:
        i) details on how local IRB approval will be obtained and maintained at each site;
        ii) description of procedures in place to ensure that the informed consent document approved by the local IRB does not have substantive changes in the purpose, procedures, and risks sections from the form approved by the CU IRB;
        iii) plan for ensuring that unanticipated problems involving risks to subjects or others will be reported to the local and CU IRBs;
        iv) plan for data and safety monitoring, including review of reports of unanticipated problems that involve risks to subjects or others, ensuring confidentiality of study data at local sites, during transmission, and at CU, analysis and dissemination of interim results;

v) process for implementing protocol modifications.

c. In addition, if the research will be federally conducted or supported:

1) the name and FWA number for each site engaged in the research;

2) an Unaffiliated Investigator Agreement (UIA) for any individual who is engaged in the research but is not working under the auspices of an institution or organization, including CU.

Processing multi-site projects, some of which may require IRB review for funding purposes long before procedures for inclusion of human subjects have been developed, requires special consideration by the administrative staff and IRB. Although projects wherein CU serves multiple roles may be submitted as one protocol for IRB review, it is often beneficial for the components to be submitted separately. This approach facilitates focused review of each component, and management of each role as appropriate to that role, e.g., the protocol for CU as a clinical site could be closed out when study procedures for all subjects are concluded, while the related repository or data coordinating center protocol for the overall project continues at CU. Consultation with IRB staff early in the development process is recommended, to identify and guide the most efficient approach.

14. Submission materials: Collaborative Research conducted under IRB Authorization Agreements

Federal regulations permit an IRB at one entity to rely on the review of an IRB at another entity in specific situations, and require that the terms of the reliance agreement be described in an executed IRB Authorization Agreement (IAA). IAAs may exist between institutions for multiple projects that meet specific criteria, between legally separate components of one institution for multiple projects, or for individual projects. All IAAs that involve CU must be approved by the appropriate IO on the applicable CU or NYP FWA and the ED.

Several Agreements exist that describe the conditions under which Columbia may rely on the IRB of another institution, Columbia will conduct reviews for another institution, or a combination thereof. The material required to be submitted to the Columbia IRB for a protocol that is subject to one of these Agreements is contingent upon the relevant IAA and may be found in Working Practice Document #05. Information about the terms of the specific agreements may be found in Working Practice Document #05.

When Columbia relies on another IRB to review protocols, there may or may not be a subsequent review by the Columbia IRB. When such a review is conducted by the Columbia IRB, it will often be a facilitated review, i.e., a review by an IRB Chair or an experienced member of the IRB to determine whether the protocol is appropriate for the local environment. Regardless of whether the relevant Agreement requires a facilitative review, protocols reviewed by other IRBs under IRB Authorization Agreements generally need to be submitted to the Columbia IRB via RASCAL for tracking purposes.

15. Submission materials: Domestic research conducted at non-CU sites

As with international sites, some domestic sites may have characteristics which are significantly different from those at CU and in the surrounding areas, and consequently present a challenge in ensuring that IRB review criteria are satisfied because IRB members may not have adequate knowledge of the local context. In some cases, such research will also be reviewed by a local IRB if collaboration between CU and local researchers is involved, and in those situations, documentation of such review should be obtained.

If local IRB review is not obtained, and a need for additional knowledge about local context is identified, the IRB may opt to obtain this information through one or more sources, including the following: a) use of a consultant who has extensive knowledge of the environment and/or population, as appropriate; b) input from a local community board or similar committee comprised of individuals who represent the locale and/or citizens; or c) literature review. Selection of source should consider the level of risk of study procedures to participants, e.g., while literature review may be acceptable for a minimal risk survey, use of a consultant or feedback from a local committee may be more appropriate for a study that poses greater than minimal risk.

Justification for selection of the particular study site should also be provided. Authorization from facilities at which study procedures will be conducted may be necessary in addition to knowledge of local context described above.

16. Submission Materials: Research Conducted at External Sites by CU Researcher

Columbia investigators who conduct research at non-Columbia sites have additional responsibilities for ensuring that all appropriate approvals from the study site(s) are obtained, and that procedures have been developed to ensure that the study may be conducted in compliance with the protocol at the external site.

In addition to the material listed in the preceding section (V.B.) related to the type of event (e.g., new protocol, renewal, modification), the following material/information is required:

- contact information for each site;
- whether each site has granted permission for the research to be conducted;
- IRB/ethics approval:
  - whether each site has an IRB and if so, whether it has approved the research; or
  - plans to enter into, or attachment of an executed, IRB Authorization Agreement whereby the site relies on the Columbia IRB.

Additional guidance:

- If the external sites are international, please refer to Section V.C.11 of these written procedures for additional guidance.

- If there will be collaboration with investigators from other institutions, please refer to Section V.C.13 and/or V.C.14 of these written procedures for relevant guidance.
- If the external sites are in the U.S., but not local, please refer to Section V.C.15. of these written procedures for guidance related to obtaining adequate knowledge of the local context.

D. Administrative review ("pre-review") of submitted events

This section provides an overview of the review phase of the process. Complete details of the process, including the criteria on which the review is based, will be found in the Review section (Section VI) of these written procedures.

Upon submission, an administrative review ("pre-review") by IRB staff is conducted. The nature of the review is contingent upon the type of event (e.g., new protocol, renewal, modification) and is described in more detail in the Review section (Section VI) of these written procedures.

As a result of the administrative review, the submission is either logged in to the Chair's queue in RASCAL or returned electronically to the researcher. If an event is returned, it will proceed through another administrative review upon resubmission. Details of the routing process and indication of which staff member conducts each step can be found in Working Practice Document #24.

Upon completion of each administrative review of new protocols submitted for the first time, the staff reviewer completes a reviewer form (Working Practice Document #34a, "Reviewer Form: New Protocols (Biomedical)" or #34b, "Reviewer Form: New Protocols (Behavioral)") and enters comments in the Notes field for the event.

A reviewer form is also completed by staff during pre-review of renewal submissions (Working Practice Document #110, "Renewal Pre-review Form"), and the termination review is guided by specific criteria (Working Practice Document #111, "Termination Return Criteria"), followed by a summary entry in the Notes field. The outcome of staff pre-review of other events (e.g., modifications, unanticipated problem reports) is entered in the Notes field.

At the conclusion of the pre-review for renewals, terminations, and unanticipated problem reports, the reviewer takes appropriate action to facilitate the event being logged in (i.e., accepted for review) or returned to the researcher for revision or additional documentation/information. The format for the commentary that is entered in the Notes section can be found in Working Practice Document #20.

E. Routing of submissions to IRB per level of review required

Submissions are routed electronically to the Chairperson's queue after being logged in by IRB staff. The Chair reviews comments entered in the Notes field relevant to each event (as a result

of the administrative review) to obtain a synopsis of the event, awareness of regulatory considerations, and recommended level of review. Depending upon the level of review required, the Chair will review the event him/herself or distribute it to an experienced Board member for review. To the extent possible, reviews after the initial approval will be conducted by the Board which originally approved the study and by the primary reviewer who originally presented the study.

1. Level of Review: Not human subjects research

During the course of the Chair review of submitted new protocols, and with consideration for the recommendations of the administrative reviewer, a determination may be made that the project does not meet the definition of research as defined in the applicable federal regulations, or the involvement of humans is such that the definition of a human subject is not met. In such cases, the Chair may label the protocol as either "not human subjects research" (i.e., definition of research is not met) or "not human subjects research per 45 CFR 46" (i.e., definition of human subject is not met), respectively. These projects are not subject to continued oversight by the IRB.

Justification that the project does not meet the criteria to be considered human subjects research must be provided, if the PI is seeking such a determination, or able to be derived from submitted materials and information. Only the Chair may select one of the "not Human Subjects Research" options in RASCAL.

If it is unclear whether research with human subjects is involved, investigators may request an administrative review of a proposal outside of the RASCAL system, to determine whether review by the IRB (and a submission in RASCAL) is required. In those cases, an IRB officer will request a copy of all available materials, and based on that information, make a determination about whether a submission to the IRB is required, i.e., whether the proposed activities constitute *research* with *human subjects.* The determination is documented in writing to the requestor, and includes a statement to the effect that the determination is applicable only to the materials submitted.

IRB staff and Board members may use the Research Decision Chart (Working Practice Document 29), or other similar tools, such as the OHRP decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm), to guide them towards the appropriate determination.

2. Level of Review: Exempt determination

Research that falls into one or more of six specific categories of research defined in the federal regulations (45 CFR 46.101(b)) may be determined to be exempt from the requirements of 45 CFR 46. Protocols for which the investigator has entered an exempt declaration and justification are reviewed by the IRB Chair, who has the capability to approve the project as exempt, designate the protocol as eligible for expedited review (if more appropriate than exemption), or

return the protocol to the investigator. The protocol will be returned if revisions, additions, or deletions are required. The Chair also has the authority and RASCAL ability to either remove an exempt declaration that was entered by the PI, or designate a protocol as exempt even if the PI has not entered an exempt declaration. When an exempt declaration entered by the PI is removed by an IRB Chair, the information that was in the exempt declaration is automatically ported to the IRB notes by the RASCAL system.

Per RASCAL functioning, the Chair may not electronically distribute events that include an Exempt Declaration. Therefore, the Chair reviews these events, or may request that another qualified individual review the material by retrieving it in RASCAL by the IRB number. The selected reviewer may enter comments in the Notes section upon completion of their review. RASCAL programming labels exempt determinations as approvals; only the Chair may electronically "approve" an exemption.

If there is any information that needs to be checked or verified with the investigator, the designated reviewer or staff may initiate this contact. Communication via RASCAL correspondence is recommended. If e-mail communication is used, the messages should be copied and pasted into the Notes section for the event being reviewed. Phone calls should be documented in the Notes if other than routine procedural information is discussed.

The exemptions apply to research with children, except for research involving survey/interview procedures that are not directly related to evaluations of standard educational practices in accepted educational settings. Exemption (2) at 46.101(b)(2) for research involving survey or interview procedures or observations does not apply to research involving children, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

Research involving prisoners is not eligible for exemption. The exemptions do not apply to research that involves an investigational drug, device, or biologic, (i.e., are subject to FDA regulations). Except for exemption 6, the exemptions do not apply to FDA regulated research.

As noted in the Columbia Informed Consent Policy (Working Practice Document #10), in the spirit of the principles of the Belmont Report, in which autonomy of the individual and the voluntariness of participating in research are fundamental ethical principles, the IRB strongly recommends that informed consent also be obtained for certain exempt studies. For exempt studies that allow for direct interaction between the investigator and human subjects, participants should minimally be informed of the following: that the activity is research, the procedures that are involved in the study, the nature of the risks (e.g., little, if any expected inconvenience or harm), that participation is voluntary and that they may withdraw from the study at any time.

Exempt decisions are communicated to the research team via RASCAL correspondence by both the CUMC and CU-MS IRBs, and, in the case of approvals, also by hard copy Letter of Approval (LOA) (Working Practice Document #93), for the CUMC IRBs only; the CU-MS IRB provides notification of exemption determinations solely via RASCAL correspondence.

Exempt determinations are valid for a period of two years. At the end of the two year period, an abbreviated renewal application must be submitted for tracking purposes. Unless the research has changed in such a manner that the project is no longer exempt, approval will be provided for an additional two year period (Working Practice Document #9).

A list of exempt determinations shall be provided to the full Board as soon as practical after such actions, via IRB minutes. Although not required from a regulatory perspective, such notification affords the IRB members the opportunity to be aware of, and provide input about, if warranted, all human subjects research that may be conducted under the auspices of the institution. The IRB Chair shall respond to questions, if raised, from the Board concerning these events.

3. Level of Review: Expedited

The Board may utilize an expedited review procedure as authorized by 45 CFR 46.110 and 21 CFR 56.110.

Upon review of a submission, if it does not meet the criteria for exemption, but the criteria for expedited review appear to be met, the Chair will designate the protocol as eligible for expedited review by selecting the appropriate expedited review category in RASCAL. The Chair will then distribute the protocol for review by selecting a primary reviewer and sending the protocol electronically to the reviewer's queue. The reviewer has access, electronically within RASCAL, to all information and documents that were submitted by the study team. A qualified member of the Board (in general, one who has one year or more of IRB experience) or the Chair may serve as the primary reviewer. If necessary to ensure the necessary reviewer expertise, additional reviewers may be selected.

In accordance with federal regulations, the designated reviewer(s) may act for the Board to approve or require changes to an event under review, and ensures that all review criteria are met. To facilitate this process, reviewers are routinely provided with tools and information to guide their review, including a primary reviewer form, decision charts, and educational information, as part of the CU IRB educational initiatives. Board action is required, however, for a decision to disapprove a study.

The Board may utilize the expedited review process for the following types of research (45 CFR 46.110; 21 CFR 56.110):

a. Minor changes in previously approved research during the period of one year or less, for which approval is authorized; a guidance document (Working Practice Document #112) has been drafted to assist in determining whether a change is minor; in addition, minor modifications are addressed in section VI.C.2. of these SOPs;

b. Research activities involving no more than minimal risk for which the only involvement of human subjects will be in one or more of the categories identified on the respective list as published by the FDA and HHS.

In reviewing the research, the reviewers may exercise all of the authorities of the Board except disapproval. If the reviewer(s) find that the protocol does not meet the criteria for expedited review, they will refer it to the full Board for action.

If there is any information that needs to be checked or verified with the investigator, the designated reviewer or staff may initiate this contact. Communication via RASCAL correspondence is recommended. If e-mail communication is used, the messages should be copied and pasted into the Notes section for the event being reviewed, or attached as Internal Documents. Phone calls should be documented in the Notes if other than routine procedural information is discussed.

The reviewer who is conducting the expedited review may enter comments in the Notes section of RASCAL and make non-RASCAL documents such as handwritten or typed comments available to the IRB staff as documentation of the review and to assist in preparation of correspondence. These documents will not be considered part of the official file unless they are attached to the protocol in RASCAL.

Three functional categories exist in RASCAL in the expedited review option list: Facilitative Review, Administrative Review of certain types of awards to support multiple projects involving numerous investigators, and review per 45 CFR 46.118. The first was developed to allow processing of protocols subject to IRB Authorization Agreements when CU is not the IRB of Record (additional detail in following section), the second was implemented to permit processing of submissions reflecting programs for which human research exists only in individual studies that will each receive IRB approval, and the third was instituted to facilitate processing of protocols for which procedures involving human subjects were not defined at the time of IRB submission (but IRB approval is required by the funding agency). See Working Practice Document #108, Email from George Gasparis to CU IRB Chairs and staff, "Addition of new expedited review category in RASCAL", for additional information regarding the Administrative Review category.

A list of research that has been approved under an expedited procedure, including an explanation of the type of research activity and the action taken, shall be provided to the full Board as soon as practical after such expedited approval, via IRB minutes. Members participating in the expedited review shall respond to questions, if raised, from the Board concerning the events approved in this manner.

The Board will not use the expedited procedure if its use of the procedure has been suspended or terminated by the FDA, OHRP or the University.

Decisions made by expedited review are communicated to the research team via RASCAL correspondence, and, in the case of approvals, also by a hard copy Letter of Approval (LOA) (Working Practice Document #93).

4. Level of Review: Facilitative/Administrative/118

A facilitative review is conducted when the IRB has agreed to rely on the review of an IRB from a non-Columbia institution, via an executed IRB Authorization Agreement. The specific review process is contingent upon the relevant Agreement.

The Boards may act in liaison with the IRBs of other institutions as necessary to assist in the approval of joint and cooperative projects involving multiple sites and/or investigators. The ED or the Boards may agree to permit another IRB listed on a CU FWA to act as the IRB of record for studies to be conducted by, or with the assistance of Columbia personnel, at the facilities of another institution. In addition, a CU IRB may agree to function as the IRB of record for another investigator and/or institution if the project involves material collaboration from Columbia personnel.

Such Agreements will require written letters of agreement and may necessitate the completion of an FWA, a UIA, or an IAA. Specific criteria for, and procedures for implementing, each of these agreements can be found on the OHRP website.

Details of the level of, and criteria for, review of protocols that are subject to each IAA can be found in Working Practice Document #05.

5. Level of Review: Full Board

Full Board review is required for any protocol that involves research with human subjects and does not qualify for exemption, expedited review, or facilitative review per the terms of an IRB Authorization Agreement.

Each protocol that requires full Board review will be assigned to a primary reviewer (explained below) who will be responsible for a full review of all materials, and will lead the discussion of the protocol at the meeting. Additional primary reviewers may be designated by the Chair. Review criteria are explained in more detail in the Review section (Section VI) of these written procedures. All members of the Board to which a review is assigned have access in RASCAL to all materials submitted by the study team, Notes entered by IRB staff and Chair, and Internal Documents attached by IRB staff or Chair.

Complete documentation of all submissions to a specific IRB is available electronically, from the time of the initial submission, for review to all members appointed to the respective Board.

As necessary to accommodate the needs of Board members, hard copies or electronic versions of review material will be distributed approximately one week in advance of the meeting to enable members to actively and constructively participate in the protocol review. Details regarding the material to be distributed, and manner of distribution, can be found in the Packet Preparation section (Section VII.B.) of these written procedures.

Alternatively, Board members will be notified electronically of the protocols under consideration, to facilitate online review.

F. Primary Reviewer system

1. Primary reviewer system: Initial review

The CU IRBs use a primary reviewer system for research that requires full Board review. Each research activity is assigned to at least one primary reviewer, based on related expertise. A reviewer who has a conflict of interest in regards to the protocol, (e.g., is a co-investigator, has provided consultation for, or has a financial interest in the sponsor or product being tested), will not be assigned as a primary reviewer, but may be asked to provide information to the Board during the review. IRB members who are listed among the personnel on a submission do not have access to the Notes entered by IRB staff and members, Internal Documents, or reviewer assignment.

When making reviewer assignments, the Chair considers the type of research and any recommendations from IRB staff, then selects a reviewer with expertise in the relevant area. It is especially important that individuals with appropriate scientific expertise serve as primary reviewers or otherwise have input to the IRB review if a project has not been peer-reviewed, either by a funding agency (e.g., NIH, NSF) or intra-departmentally (e.g., Herbert Irving Comprehensive Cancer Center, Department of Pediatrics).

When necessary to ensure a substantive review of the protocol, more than one reviewer may be assigned to evaluate a given protocol. An individual Board may elect to assign more than one primary reviewer for all protocols.

When additional expertise is needed that is not available among members of the Board conducting the review, consultants may be used, or the protocol may be assigned for review to another Board that has the appropriate expertise.

If vulnerable populations are involved in the research, the Chair attempts to assign the protocol to an IRB member with experience dealing with the specific vulnerable population or, in the case of full Board reviews, ensures that an individual with such knowledge or experience will be at that meeting at which the submission is reviewed. The Chair may assign a protocol to him/herself, another primary member, or an alternate member.

A prisoner representative is assigned to review each protocol that involves prisoners as subjects. The Chair may determine that protocols which involve subject populations for which the potential for incarceration during the course of participation in the trial is high should be reviewed as a prisoner protocol, to avoid disruption of participation or the need for re-review if a subject should become a prisoner. The reviewer is guided by the Prisoner Research review form (Working Practice Document #94).

Primary reviewers are responsible for conducting an in-depth review of all available documentation and presenting the study to the Board, if the submission requires full Board review. All members have electronic access to the complete submission of all protocols assigned to the Board of which they are a member, whether regular or alternate.

2. Primary reviewer system: Continuing review (renewal)

The Chairman will select a primary reviewer (him/herself, another regular member of the IRB, a consultant, or an alternate member) and distribute the renewal request within RASCAL to that individual, if he/she is a member of a CU IRB. As for new protocols, the Chair will select a primary reviewer who has the appropriate expertise to review the submission. Information that is available electronically, and should be reviewed by a primary reviewer, will be provided by the most appropriate means (e.g., in hard copy or electronically) to any consultant who would not normally have access in RASCAL.

An attempt will be made to assign the protocol to the Board member who reviewed the initial submission or the most recent renewal request.

The reviewer has access to the complete historical file (i.e., where applicable, the paper file that was in existence before the conversion to RASCAL) for the study as well as all renewal information during his or her review and may request that specific information be provided to all Board members prior to the convened IRB meeting (for those studies that require full Board review). All members have electronic access to the complete renewal submission in RASCAL and all preceding submissions for the protocol that are in RASCAL.

A prisoner representative is assigned to review each protocol that involves prisoners as subjects. The Chair may determine that protocols which involve subject populations for which the potential for incarceration during the course of participation in the trial is high should be reviewed as a prisoner protocol, to avoid disruption of participation or the need for re-review if a subject should become a prisoner. The reviewer is guided by the Prisoner Research review form (Working Practice Document #94).

3. Primary reviewer system: Modifications, Unanticipated Problem reports

The Chairman will select a primary reviewer (him/herself, another regular member of the IRB, a consultant, or an alternate member) to receive the electronic submission. As for new protocols, the Chair will select a primary reviewer who has the appropriate expertise to review the submission.

An attempt will be made to assign the event to a Board member who reviewed the initial submission or the most recent renewal request.

Consultants may also be used when the requisite expertise to assess the information provided cannot be provided by available Board members.

Information that is available electronically, and should be reviewed by a primary reviewer, will be provided by the most appropriate means to any consultant who would not normally have access in RASCAL.

All Board members receive a copy of the Report of the Unanticipated Problem, Notes field affiliated with the event (which includes pre-reviewer notes), and supporting documentation attached by the researcher. The assigned primary reviewer(s) for the event and the Chair receive, in addition to the material distributed to all Board members, a copy of the Data Sheet, and current Informed Consent Forms.

The reviewer has access to the complete historical file (i.e., prior submissions and IRB actions) for the study during his or her review and may request that specific information from the historical file be provided to all Board members prior to the convened IRB meeting (for those studies that require full Board review). All members have electronic access via RASCAL to the complete modification or Unanticipated Problem Report submission.

The Board will determine, based in part on the primary reviewer's recommendation, whether the report is complete or additional information is required. In addition, a determination will be made of whether the protocol and/or consent document(s) should be revised, if this is necessary as a result of the UP and has not already been initiated by the study team. When revision to the consent form(s) is deemed necessary, the Board will determine whether currently enrolled subjects also need to be informed. Finally, the Board may impose restrictions on the research (e.g., more frequent reporting, suspension of enrollment, suspension of the study, termination, etc.) if review of the unanticipated problem report results in a determination that the risk/benefit ratio has become less favorable.

Details of all review processes are in Section VI, IRB Review of Human Subjects Research, of these written procedures.

G. Post-Review Procedures

Minutes will be generated to reflect actions taken by the Board during convened meetings. The minutes of IRB meetings will document separate deliberations, actions, and votes for each event undergoing review by the convened IRB, as well as a summary of any Board discussions of controverted issues.

Notification to the Board of actions taken by the Chair or designated reviewers in-between meetings occurs via inclusion in the agenda and minutes of subsequent meetings. Details of the process by which minutes are generated can be found in the Minutes (Section VII.E.) section of these written procedures.

H. Notification to Researcher: General Process

Outcomes of all reviews will be communicated to researchers as expeditiously as possible after the review is complete. Minutes of full Board meetings will usually be approved in their entirety prior to transmittal of the correspondence via RASCAL related to the outcome of an event reviewed at the meeting.

Minutes for the entire meeting need not be approved before the correspondence for an individual item is sent, provided the minutes for that item are approved (through documented contact with the Chair outside of RASCAL or via use of the Immediate Action feature in RASCAL). A hard copy LOA (Working Practice Document #93) is also generated to document IRB approval.

The Boards will follow HHS and FDA regulations for reporting its findings and actions to the investigator, and when applicable, to the institution (45 CFR 46.108; 46.103(b)(4); 46.103(b)(5); 21 CFR 56.108 (a)(1)). In cases where the protocol is not approved as submitted, specific requests and concerns of the reviewer and/or Board, as appropriate to level of review, will be communicated to the study team via RASCAL. Wherever possible, guidance as to an acceptable response and the basis for the requests or concerns are included.

1. Notification: Approval and Outcome of Review

All requests and concerns of the IRB, whether from a full Board or expedited review, or evaluation to determine whether exemption is appropriate, must be addressed satisfactorily by the research team before a protocol may be approved or receive an exemption determination.

For expedited and exempt reviews, correspondence to the research team will initially be generated and transmitted in RASCAL via the correspondence function for each action taken by the Board, Chair, or designated reviewer. IRB staff will evaluate the correspondence for completeness and accuracy, revise as necessary to include regulatory or institutional requirements, and forward the correspondence to the Chair for electronic transmittal to the research team. See Working Practice Document #95 for an explanation of the members of the research team to whom correspondence is sent within RASCAL.

For full Board reviews, correspondence for each individual event that was indicated on the agenda will be automatically transported from the minutes, when approved, to the correspondence queue, where IRB staff will then conduct an evaluation for completeness and accuracy, add regulatory or institutional requirements, if necessary, and forward the correspondence to the Chair for electronic transmittal to the research team.

Approval of a non-exempt research activity will also be documented and communicated by means of a hard copy LOA which will be sent to the PI. The LOA will reflect the approval provided electronically by the Chair/designee or authorized expedited reviewer, and must be signed by a designee with signing authority. This authority is limited to IRB Chairs, the ED, AD and Managers; letters are usually signed by the Manager.

Letter templates (Working Practice Document #93) are used to ensure consistency of format and inclusion of specific elements.

The LOA used for initial and continuing approval of a protocol will contain information about the study and its approval status. This document includes:

a. title of the research project;

b. name of PI;

c. for funded projects, funding award number and protocol version number, if available;

d. level of IRB review;

e. approval and expiration dates;

f. consent requirements;

g. approved study-related material that will be provided to subjects;

h. conditions to the approval, e.g., requirement to translate consent documents;

i. approved HIPAA forms; and

j. information regarding continuing review requirements, reporting of unanticipated problems, and the need to submit modifications for approval prior to implementation.

The LOA for changes in an approved research project will include, in addition to the items noted above:

a. a description of the modification; and

b. consent requirements, if revised from the originally approved procedures.

All LOAs will indicate to whom copies (if any) will be sent. Letters for protocols that involve cancer-related research will be copied to the Cancer Center Protocol Office. Letters for research approved under an IAA may be copied to the IRB office of the institution with which the agreement was signed, depending upon the procedures applicable to the respective Agreement.

2. Notification: Disapproval

Correspondence will be sent to the research team electronically via the RASCAL correspondence function. See Working Practice Document #95 for an explanation of the members of the research team to whom correspondence is sent within RASCAL.

Disapproval of research may only be determined by the convened Board, and the action will be documented in the minutes for the meeting. Documentation of the outcome of the review will be communicated by means of a hard copy Letter of Disapproval (LOD) (Working Practice Document #96) which will be sent to the PI. The LOD will reflect the disapproval issued electronically by the Chair/designee and must be signed by a designee with signing authority. This authority is limited to IRB Chairs, the ED, AD and Managers.

The LOD must include the reason that the research, or research procedures, was/were disapproved. This document will also include:

a. title of the research project;

b. name of PI;

c. description of the process through which the investigator may address the Board in person or in writing regarding its action;

d. contact information for the IRB.

A letter template (Working Practice Document #93) is used to ensure consistency of format and inclusion of specific elements.

All LODs will indicate to whom copies (if any) will be sent. Letters for protocols that involve cancer-related research will be copied to the Cancer Center Protocol Office. Letters for research approved under an IAA that may be copied to the respective institution's IRB office with which the agreement was signed, depending upon the procedures applicable to the respective Agreement.

3. Notification: Suspension

Correspondence will initially be sent to the PI either by email or hard-copy letter, and may follow via RASCAL correspondence. See Working Practice Document #95 for an explanation of the members of the research team to whom correspondence is sent within RASCAL. Documentation of the non-RASCAL notification will be entered in the Notes section of the protocol or as an attached document in RASCAL.

The PI's Department Chair and/or Division Chief, as appropriate, and the relevant IO will be copied on the letter.

Notification of all suspensions will also be forwarded to OHRP and, as appropriate, to any other regulatory agency(ies).

I. Documentation of review and approval

Documentation of actions taken by the Chair or other authorized reviewer(s) in RASCAL will be retained electronically within the RASCAL system.

All IRB members are provided with a checklist of the IRB review criteria (45 CFR 46.111 and 21 CFR56.111) to guide them through reviews, as these must be satisfied before a new, ongoing, or modified non-exempt protocol may be approved. See Working Practice Document #109 for a copy of this checklist. The approval of a new, ongoing, or modified protocol via an expedited review process indicates that the reviewer has considered all of the criteria and ensured that they are met. When full Board review is required, the affirmative vote of the IRB to approve a protocol, either outright or when specific items have been addressed, reflects that the primary reviewer's comments have been considered and the IRB review criteria have been satisfied.

Correspondence related to IRB actions that is generated within RASCAL will also be stored electronically within the electronic system.

Consent documents generated within RASCAL, using the consent form builder function, will be stamped as approved electronically when the status of the event changes to "approved". Please refer to Working Practice Document #161, Exceptions to Automatic Consent Form Stamping, for a current list of situations for which a consent form will not automatically receive an approval watermark when the event to which it applies is approved.

Consent documents, including recruitment material and study instruments that are generated outside the system but attached in RASCAL will be printed by IRB staff and stamped manually with the IRB approval stamp.

Both the RASCAL and manual approval stamps indicate that the document has been approved by the Board, and shows the expiration date. The stamp is only used on finalized documents, and will appear on each page of the consent form and recruitment material; study instruments, if voluminous, will only be stamped on the first page of the document. The manual stamp will also include the IRB number, the initials of the staff member who affixed the stamp, and the approval date.

The approval stamp will be applied to the document only when the Board action has been completed. Documents may not be stamped in advance of the approval.

VI. IRB Review of human subjects research

This section describes how the IRB determines whether an event that has been submitted should be approved. Each variable (e.g., type of event, type of research) is described individually and is provided as guidance for use in the review process. Investigators should be familiar with the criteria for review for their particular type of research, and event submitted, to facilitate the inclusion of all necessary information in the submission. The IRB will consider all applicable factors for a given submission. For example, if a submission is for a new protocol that involves an investigational drug administered to children, the information described in each of the relevant sections (i.e., new protocol, drug study, and minors) will be evaluated.

The IRB will conduct a review of non-exempt research in accordance with 45 CFR 46, New York (NY) state law, and institutional policies, and ensure that all elements of 45 CFR 46.111 are met prior to approval of the research. When the research involves FDA regulated drugs, devices or biologics, the IRB will also consider the applicable parts of Title 21 of the Code of Federal Regulations [21 CFR 50, 56, 312, 600, 812].

Review of all research involving human subjects, including exempt research, must ensure that all new personnel have completed the appropriate web-based human subjects training course available in RASCAL. Individuals must complete both Human Subject Protect training and research-related HIPAA courses if they are affiliated with the CUMC campus or are conducting research that involves the creation, use, or disclosure of Protected Health Information (PHI).

Specific detail regarding review of each type of event (e.g., new protocol, modification, renewal) is in the event-specific section of these written procedures (Section C).

Protocols that meet the criteria for exemption will initially be pre-reviewed by IRB staff, then reviewed by the IRB Chair.

Research involving procedures that fall within one or more of the allowable categories for expedited review will initially be pre-reviewed by IRB staff, then reviewed by the IRB Chair or an experienced Board member, as designated by the IRB Chair. In accordance with federal regulations, the designated reviewer(s) may act for the Board to approve or require changes to a study under review. Board action is required, however, for a decision to disapprove any study.

Protocols that do not meet the criteria for exemption or expedited review will initially be pre-reviewed by IRB staff, then reviewed at a convened meeting of the IRB. This process is described more fully in Section VI, “Process”.

At each step of the review process, the event under review is assigned a specific status (e.g., approved, pending, returned, deferred) to reflect the action of the researcher, staff, or Board, as applicable. See Working Practice Document #04, Actions of the IRB, for specific terms and the description of each.

“IRB review” in these policies and procedures, unless specified otherwise, refers to: a) review by the convened Board when full Board review is warranted; and b) review by an experienced IRB

member when submissions undergo an expedited review. Similarly, when referring to "the IRB" in reference to review processes, the phrase means the convened IRB for full Board reviews and an experienced IRB member for expedited reviews.

A. Administrative Review ("Pre-review") of Submitted Events

Upon submission of an event (e.g., new protocol, modification, renewal, unanticipated problem report, termination) in RASCAL, an administrative review ("pre-review") by IRB staff is conducted. Depending upon the nature of the event, the process may differ but will result in all cases with a decision to either log it in (accept the submission for review), or return it to the research team to obtain missing information and/or documentation. Details of the process for each type of event are described below.

1. Administrative Review ("Pre-review"): New Protocols

New protocols are pre-reviewed for completeness and compliance with applicable policies and statutes. The staff reviewer determines whether the protocol is complete and should be logged in or needs to be returned for additional information, enters comments about the protocol in the Notes section of RASCAL for consideration by the Board reviewer, completes a reviewer form, attaches the reviewer form to the protocol in RASCAL, and recommends a level of review based on federal regulations and institutional policy.

At this stage, protocols will be returned only for the following criteria:

a. PI is not qualified, no one is named as PI, more than one individual is named in this role, or PI's privileges are suspended by the IRB;
b. sponsor's protocol, investigator's brochure, device manual or other component of the formal description of the research is missing;
c. grant application or other documentation of funded procedures is not included, for funded projects;
d. consent documents are not included, and a waiver of informed consent is not requested;
e. study instruments are mentioned but not included;
f. there is no plan for recruitment;
g. there is no data safety monitoring plan and the study is greater than minimal risk
h. there is not enough information to conduct an adequate review.

Details of the pre-review process are included in Working Practice Document #20 and in Section V.D. of these written procedures.

2. Administrative Review ("Pre-review"): Renewals

Renewals are pre-reviewed for completeness, progress since initial approval, and compliance. The staff reviewer determines whether the renewal is complete and should be logged in or returned, assesses whether enrollment is ongoing, determines whether previous IRB conditions have been met, enters comments about the progress of the protocol in the Notes section of RASCAL for consideration by the Board reviewer, completes a reviewer form, attaches the reviewer form to the renewal in RASCAL, and recommends a level of review based on federal regulations and institutional policy.

At this stage, renewals will be returned only for the following criteria:

a. enrollment status is not provided, and/or information regarding enrolled subjects is not included;

b. enrollment is ongoing, consent forms are not attached, and a waiver of informed consent is not requested;

c. PI is not qualified, no one is named as PI, more than one PI is named, or the PI has had his/her research privileges suspended by the IRB;

d. sponsor's protocol, investigator's brochure, device manual, grant, or other component of the formal description of the research is missing;

e. a summary of unanticipated problems, or recent report of a data and safety monitoring body, is not included, where applicable;

f. Child Involvement section is required but missing;

g. Cancer Center review is required, but Cancer Center is not listed under Research Facilities;

h. IBC Appendix C is required, but is not attached;

i. Investigational Product section is blank and there is an investigational product.

IRB staff will use their professional judgment to evaluate the date of expiration of IRB approval versus the ability to obtain missing information by returning the submission to the investigator. When the IRB review may proceed with enough information to evaluate the progress of the study and the IRB approval for the study has expired, or will expire in the near future, the IRB staff will not return the submission to the investigator, but rather attempt to obtain the missing information outside of RASCAL. Whenever missing information cannot be obtained for studies with expiration of IRB approval imminent, the IRB staff will note the missing information and the IRB will proceed with a review, at least for subjects currently enrolled.

Details of the pre-review process are included in Working Practice Document #20 and in Section V.D. of these written procedures.

3. Administrative Review ("Pre-review"): Modifications

Modifications are pre-reviewed initially by staff and a brief summary of the requested modification is entered in the Notes section. The staff reviewer also indicates whether the consent form has been modified, assesses whether enrolled subjects need to sign new consent forms, and makes a preliminary assessment of whether the modification can be reviewed by expedited review (if changes are not substantive) or requires full Board review.

The intent of the summary is to provide the Chair with the basic information needed to process the modification request, by distributing it to a Board reviewer or him/herself. If the submission is incomplete, i.e., all necessary information or documentation to support the changes or additions is not submitted, it will be returned by the staff reviewer.

Guidance is provided on what constitutes a substantive change in Working Practice Document #112, "Modifications: What Constitutes a Substantive Change?".

4. Administrative Review ("Pre-review"): Unanticipated Problem Reports

Reports of Unanticipated Problems are pre-reviewed by IRB staff to ascertain whether they meet the criteria in the CU Reporting to the IRB of Unanticipated Problems policy (see Working Practice Document #02).

Reports that do not meet the criteria are returned with instructions to withdraw the report or provide justification for how it does meet the criteria and therefore, should be reviewed by the IRB.

Unanticipated Problem reports that meet the criteria will be logged in (accepted for review). The staff reviewer may also review the current consent document to be able to recommend whether changes need to be made to satisfy regulatory review criteria, if the researcher has not provided such an assessment, or the assessment appears incomplete or inaccurate. The staff reviewer will enter comments in the Notes field to reflect the pre-review findings.

Summary material provided by the study team in the Unanticipated Problem report, and the staff reviewer's comments, are provided to the Board members; the primary reviewer and Chair receive additional material (details can be found in Section VII.B.4.). At the Board meeting, the primary reviewer's recommendations, based on a comprehensive review of all available information and the administrative review comments, will be considered by the convened IRB before determinations about completeness of the report, and whether changes to the protocol or consent documents are necessary, are made.

Details of the pre-review process are included in Working Practice Document #20 and in Section V.D. of these written procedures.

5. Administrative Review ("Pre-review"): Termination Reports

Termination Requests are pre-reviewed by IRB staff to verify that all information requested in the Termination Report has been submitted, and to make a preliminary assessment of whether there are any outstanding issues that need to be addressed prior to termination of IRB oversight. Outstanding issues may include: receipt of a final report, whether any harms to subjects occurred for which resolution has not been reached, or decisions related to research that may have been conducted during a lapse in IRB approval. Incomplete submissions will be returned.

The staff reviewer will use the Termination Return Criteria (Working Practice Document #111) to guide the pre-review, and enter comments in the Notes field to reflect the pre-review findings. Details of the pre-review process are included in Working Practice Document #20 and in Section V.D. of these written procedures.

B. IRB Criteria for Review

Each Board, or authorized reviewer, the latter in the case of expedited reviews, must determine that the following requirements are satisfied before research can be approved.

These criteria, as defined in 45 CFR 46.111 and 21 CFR 56.111, will be considered during the review process for each non-exempt event submitted for review. A detailed discussion of how each criterion is evaluated is provided immediately after the list of review criteria.

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.

5. Informed consent will be appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27.

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

In addition, IRB review will consider the following, as applicable:

8. Recruitment methods and advertising material are appropriate.

9. Additional protections are in place for vulnerable subjects.

10. Potential conflict of interest of investigators is eliminated, mitigated or managed.

The following section provides details of how the Boards will review each element described above.

1. Risks to Subjects are Minimized

This criterion is met by first determining all potential risks (including physical, social, emotional, and those related to breach of confidentiality) in the research study based on prior data or other relevant information. The review of risks begins with contemplation of the potential harms described by the investigator in the RASCAL submission. Then, the IRB reviewer must also consider, based on his/her knowledge and experience, risks that may not be described in the protocol submission. In particular, for all studies that involve greater than minimal risk, the IRB will consider whether each protocol includes provisions by which risks to subjects are minimized and consider any methods which may decrease risk.

Risks to subjects may be minimized by:

a. using procedures which are consistent with sound research design;
b. using procedures which do not unnecessarily expose subjects to risk, such as reducing or eliminating an exposure;
c. whenever appropriate, using procedures already being performed on the subjects for diagnostic or treatment purposes (45 CFR 46.111(a)(1); 21 CFR 56.111(a)(1));
d. increasing monitoring of the subjects for earlier detection of risks or harms;
e. adding endpoints to the study to reduce further exposure.

At the time of initial review, an IRB will classify the risk level of each protocol reviewed at a convened meeting, based on information provided in the submission and knowledge/experience

of Board members, as minimal risk or greater than minimal risk. Consideration is given to all measures taken to minimize risk when making the risk level determination.

By definition, protocols that are approved via expedited review under one of the federally designated expedited review categories may present no more than minimal risk to subjects. (Nota Bene: Based on OHRP guidance, CU IRBs interpret expedited review category 8.a. as allowing greater than minimal risk research to be approved via this mechanism, if all other criteria for the category are met.)

At each subsequent review, the Board will also consider the status of the protocol and reported unanticipated problems, and will carry the initial determination forward unless noted otherwise in the IRB record.

Level of review required may change upon subsequent reviews if the risk level changes, e.g.:

a. if the initial submission qualified for expedited review, and a modification increased the risk level to greater than minimal, the protocol would then require full Board review;
b. if the initial submission required full Board review, and procedures were limited to data analysis of long-term follow-up at the time of continuing review, the protocol could then be reviewed under an expedited review procedure.

2. Risk/Benefit Ratio is Acceptable

The IRB will approve a protocol only after it is assured that the risks to subjects are reasonable in relationship to anticipated benefits, if any, to subjects, and to the importance of the knowledge that may be expected to result.

The analysis of risks is described in the preceding section. The analysis of benefits is based on the information submitted by the investigator as well as reasonable potential benefits that may be considered by the reviewer, and Board, as appropriate to level of review.

In evaluating risks and benefits, the Board should consider only those risks and benefits that may result from the research as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research. The Board should not consider possible long-range effects of applying knowledge gained in the research (e.g. the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility (45 CFR 46.111(a)(2); 21 CFR 56.111(a)(2)).

Evaluation of the scientific design of a proposal is not the primary function of the IRB. The extent to which a Board will consider the soundness of the design is dependent upon a number of factors:

- When a protocol has undergone a peer review or equivalent process (e.g., for NIH or NSF funding), the IRB will generally accept that the design is sound.

- For some units within CU, scientific design is conducted internally, and the IRB may accept the approval of those internal review committees as evidence of sound scientific design.
- When there is an IDE or IND for the study, the IRB may consider the scientific scrutiny of the FDA as confirmation of scientific merit.
- For investigator-initiated unfunded projects, which inherently lack such a process, unless they have been reviewed by the FDA for the purposes of an IND or IDE application, the IRB must consider the design, to the degree necessary to ensure that statistically valid results may be possible.

In all cases, where the design is such that no generalizable results may emerge, and subjects are placed at risk due to to participation, the IRB may not approve the protocol until the design is revised to effect an acceptable risk/benefit ratio.

Nota Bene: When fully implemented in 2009, the CU IND/IDE Assistance Program will provide regulatory and monitoring guidance for protocols that involve an IND or IDE held by the Principal Investigator. The Standard Operating Procedures of the Program (Working Practice Document #208) describe the process, which focuses on a review by the Medical Director of the CTO of drug and device trials for which either: a) the IND or IDE is held by the PI; or b) there is no IND or IDE referenced in the submission. A primary objective is to ensure that an IND or IDE is obtained where necessary, that the PI-sponsor understands the responsibilities of these dual roles, and that guidance may be provided if necessary throughout the trial to ensure regulatory compliance. This review will supplement the IRB's evaluation of the protocol, including input regarding scientific merit, and oversight monitoring of the study.

3. Selection of Subjects is Equitable

The Board will determine that selection of subjects in each protocol is equitable, taking into account the purposes of the research and the setting in which the research will be conducted.

At the time of initial review, the characteristics of the anticipated subject population (e.g., ethnicity, race, gender, or vulnerable population) must be considered to ensure that one group does not assume the risks of the research while another group accrues the benefits.

Special consideration must be provided for the recruitment of vulnerable populations such as children, prisoners, pregnant women, and mentally disabled persons, so that their enrollment and participation in the study is not adversely affected by their vulnerability.

Renewal submissions must include demographic information for enrolled subjects, or a clear rationale for exclusion of this information. With this information, the IRB may assess whether recruitment procedures need to be revised to ensure that the initially proposed demographics are met, or consider whether the demographic characteristics of the total anticipated study population should be revised. In the latter situation, the IRB must also determine whether the objectives of the study may still be met.

4. Informed Consent Process is Appropriate

Legally effective informed consent must be obtained from every participant in human subjects research unless the requirement has been waived by the IRB in accordance with 45 CFR 46.116(c) or (d), or 21 CFR 50.24. Legally effective informed consent is not fully defined by federal regulations and therefore, state law must also be considered. The definition of human subjects research differs between the federal regulations and New York State Law in a manner that the state law more narrowly defines human research activities.

Hence, Columbia's policy for obtaining legally-effective informed consent for participation in human research is based on HHS regulations (45 CFR 46), FDA regulations (21 CFR 50), New York State Law, and the ethical principles articulated in the Belmont Report.

Both the HHS and FDA regulations for the protection of human subjects require that legally-effective informed consent is obtained from every subject enrolled into a study. The federal regulations require that each subject provides informed consent in a process that provides an understanding of the purpose, procedures, risks, benefits, alternatives to participation, confidentiality, compensation for research related injuries (for research greater than minimal risk), contacts for questions regarding the study, injuries, and rights as a research subject, and that participation is voluntary. CU IRBs evaluate each consent form in light of the federally postulated elements of consent.

The regulations further state that additional elements should be included as appropriate. For clinical trials that involve greater than minimal risk, the CU IRBs generally require the inclusion of a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

Also, when study subjects will be compensated for their participation, and study procedures involve more than one session or visit, the IRBs will evaluate the payment schedule to ensure that participants do not feel pressured to remain in a study to completion solely to obtain the compensation. Pro-rating of the compensation per study visit is the standard method of distributing the compensation fairly. Regardless of the number of study visits, the amount of compensation must be described in the consent process and reflected in consent documents, as applicable.

Further details of the elements of consent and related information about the process of informed consent can be found at: <http://www.cumc.columbia.edu/dept/irb/policies/index.html>.

The regulations require that "an investigator shall seek such consent only under circumstances that provide the prospective subject or the representative with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative."

New York State Law for human research, like the regulations, also requires that written informed consent must be obtained prospectively from every subject involved in research. There are no provisions for waiver of informed consent in the New York State Law. However, New York State Law defines human research differently than the federal regulations in such a manner that it only applies to research that involves medical experimentation or research that involves medical procedures or treatment on humans. Therefore, research that solely involves questionnaires, surveys, or epidemiological methodology is not covered under New York State Law; hence, informed consent is not required per these statutes. (However, these types of research procedures may be included in research that meets the criteria to be considered human subjects research per the federal regulations for the protection of human subjects. Informed consent, in accordance with the applicable federal regulations, would be required in these situations unless appropriately waived.)

The IRB will consider both the process of obtaining consent and the content of the process as provided in the consent form, information sheet, verbal consent script, or assent form, as appropriate.

Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with 45 CFR 46.116, 21 CFR 50, New York State Law, and as outlined in these written procedures.

During the review process, if the IRB submission does not include specific information about surrogate consent issues, attempts to obtain this information may include accessing hard copy or online resources, asking the study team to obtain the necessary information, securing a consultant with expertise about surrogate consent or the study location, or contacting IRB administrators at institutions located near the study site. When necessary, CU General Counsel, other appropriate legal sources, or a legal authority local to the study area will be contacted for clarification regarding age of majority or qualifications to serve as a legally authorized representative.

The investigator will submit a draft consent form for the Board's review as part of the initial submission, when appropriate to the research procedures. The Board or designated expedited reviewer will indicate any necessary changes to the consent form at the Board meeting or will document them within RASCAL, as appropriate to the level of review. If revision is necessary, IRB staff will generate correspondence to the investigator in RASCAL of the changes that need to be made to the consent form, and the correspondence will be forwarded to the Chair for transmission to the researcher. The investigator will make the required changes to the consent form, and return the corrected consent documents to the Board for confirmation. The confirmation may be made by the Chair or by an assigned expedited reviewer, if the changes were specific and the event was deferred back to the Chair or primary reviewer. If the changes are substantive, and the event was deferred back to the Board, the consent will be reviewed at a Board meeting. At any time, the Chair or Board member who is conducting an expedited review, or is reviewing a resubmission of an event that was deferred back to the Chair or primary reviewer, has the authority to require that consent forms be discussed at a full Board meeting.

a. Consent from Non-English Speaking Subjects

When non-English speaking subjects will be enrolled, the Board must ensure that each subject is presented with the required information in a format that he/she can understand. Specific information regarding the requirement for translation of consent documents may be found in the "Review of Research involving Non-English Speaking Subjects" section of these written procedures.

b. Consent for Audio- and Videotaping

To ensure informed consent, when study procedures involve audio- or videotaping, subjects must be advised of this detail during the consent process. The confidentiality, use and storage of the recording must be included in the consent form and, depending upon whether the recording is a required or optional procedure, a separate signature may be required. See Working Practice Documents #16 and #17, Audio- and Videotaping Policy and Sample Audio-/Videotaping Addendum, respectively.

c. Waiver of Some or All of the Elements of Informed Consent

The Board or expedited reviewer may waive the requirement for informed consent per 45 CFR 46.116 (d) (or allow an alteration of some or all of the elements of informed consent) only if all of the conditions of one of the two allowable options is met:

Option 1:
To waive consent, the Board or expedited reviewer must find and document that:

1) the research involves no more than minimal risk to subjects; and
2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and
3) the research could not practicably be carried out without the waiver or alteration; and
4) whenever appropriate, the subjects will be provided with additional pertinent information after participation (45 CFR 46.116(d)).

Option 2:
To waive consent, the Board or expedited reviewer must find and document that:

1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
   i) public benefit or service programs;
   ii) procedures for obtaining benefits or services under those programs;
   iii) possible changes in or alternatives to those programs or procedures; or

iv) possible changes in methods or levels of payment for benefits or services under those programs; and

2) The research could not practicably be carried out without the waiver or alteration (45 CFR 46.116(c)).

Informed consent may also be waived in emergency research projects that meet the criteria described in 21 CFR 56.104 (see Section V.C.4). OHRP guidance dated October 31, 1996 clarifies OHRP's position regarding waiver of the applicability of the 45 CFR Part 46 requirement for obtaining and documenting informed consent for a strictly limited class of research, involving research activities that may be carried out in human subjects who are in need of emergency therapy and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, no legally effective informed consent can be obtained. This waiver, which provides a third route through which IRBs may approve research in this class, took effect November 1, 1996.This guidance is posted online at: http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm.

In situations where some or all elements of informed consent are waived, IRB records will document the waiver and the basis for the waiver. For full Board reviews documentation will be in the minutes of the IRB meeting at which the review took place, and for expedited reviews, documentation will be in the Notes, the reviewer approval correspondence, or in an attached document. When justification for a waiver is provided in the submission by the study team, and the submission is approved without notations that indicate the waiver is not approved, approval will serve as documentation that the reviewer(s) concurred with the rationale and approved the waiver.

Waiver of informed consent is different than waiving the requirement of documentation of informed consent, described in item 5 of this section of these written procedures.

d. Enrolling Illiterate Subjects

When there is the prospect of enrolling illiterate subjects, Columbia endorses procedures that incorporate the recommendation of the FDA as articulated in the FDA Information Sheets (9/98):

> A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

5. Documentation of Informed Consent is Appropriate

Use of a written consent form that requires a signature from the subject is the usual means of documenting agreement to participate in studies that involve human subjects. The form generally includes information about the consent process (i.e., describes that the prospective subject should have the opportunity to ask questions and have them answered prior to agreeing to participate), in addition to required elements of consent, and the signed document, which represents the subject's decision, becomes a record of that agreement for both the research team and the subject. Procedures usually provide for subjects to receive a copy of the consent form as well. In clinical studies that involve in-patients, documentation of the subject's agreement to participate in a research study should also be documented in the medical record. The IRB will determine that the protocol includes procedures to ensure that informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117 and 21 CFR 50.27.

In certain specific situations, the requirement for written documentation of informed consent, parental permission, or assent may be waived, as described below.

a. Waiver of Written Documentation of Consent

The Board, or expedited reviewer, may waive the requirement that some or all subjects or the subject's representative sign a written consent document if it is determined that:

1) the research presents no more than minimal risk of harm to subjects; and

2) the research involves no procedures for which written consent is normally required outside the research context (46 CFR 45.117(c)(2); 21 CFR 56.109(c)(1)).

If the Board waives the requirement of documentation of informed consent as identified above, it may require the investigator to provide subjects with a written statement describing the research, and providing appropriate elements of consent (46 CFR 45.117(c)(2); 21 CFR 56.109(d)(2)). This decision will be documented in IRB records.

For research under HHS jurisdiction, but not FDA jurisdiction, the Board may also waive the requirement for a signed written consent document if:

1) the only link between the subject and the research would be the consent document; and

2) the principal risk would be potential harm resulting from a breach of confidentiality (46 CFR 45.117(c)(1)).

In these situations, the existence of a consent form that describes a study and includes the subject's signature may present a significant risk of harm to the subject, due to the potential for breach of confidentiality, and the IRB has the option to approve a consent procedure that utilizes either an information sheet or oral presentation of information to the subject rather than a signed consent form.

In these cases, IRB records will document that the requirement to obtain written documentation of informed consent was waived. For full Board reviews documentation will be in the minutes of the IRB meeting at which the review took place, and for expedited reviews, documentation will be in the Notes, the reviewer approval correspondence, or in an attached document. When justification for a waiver is provided in the submission by the study team, and the submission is approved without notations that indicate the waiver is not approved, approval will serve as documentation that the reviewer(s) concurred with the rationale and approved the waiver.

6. Data and Safety will be Monitored

The Board will determine that there are adequate provisions in the research plan, where appropriate, for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6)).

Plans for interim monitoring of cumulative reports of unanticipated problems involving risks to subjects or others, including adverse events, will be assessed at the time of initial review.

For research involving therapeutic intervention(s), the IRB will evaluate the safety monitoring plan. If the research is greater than minimal risk, the IRB will also consider whether a Data and Safety Monitoring Board or a Data and Safety Monitoring Committee should be required. In some cases, a committee constituted by the research team or sponsor is acceptable; in others, the IRB may find that a monitoring body comprised of individuals with no affiliation to the researchers or sponsors is necessary. Level of risk, potential for financial gains, and ability of the researchers and/or sponsors to objectively monitor the safety and data are factors that must be considered.

The following general guidelines* provide a framework for determining the appropriate level of monitoring, but are not intended to be absolute or proscriptive. Adequacy of the monitoring plan will need to be determined relative to the specific protocol under review.

MONITORING TYPE	**STUDY CHARACTERISTICS**
INDIVIDUAL INVESTIGATOR	• **STUDY POPULATION IS SMALL** • **NARROW RANGE OF FACTORS THAT COULD HAVE A SIGNIFICANT IMPACT ON RISKS AND BENEFITS** • **CONTINUOUS, CLOSE MONITORING BY THE STUDY TEAM IS POSSIBLE** • **PHASE I AND SOME PHASE II TRIALS**
DATA MONITORING	• **DEATH OR SEVERE DISABILITY IS NOT A**

COMMITTEE OR EQUIVALENT	LIKELY CONSEQUENCE OF PARTICIPATION
(MORE THAN INDIVIDUAL INVESTIGATOR BUT LESS FORMAL THAN A DATA AND SAFETY MONITORING BOARD AS DESCRIBED BY THE NCI IN 1999)	• **LOW TO MODERATE RISK RESEARCH** • **MANY INDUSTRY-SPONSORED MULTICENTER TRIALS**
DATA AND SAFETY MONITORING BOARD	• **MODERATE TO HIGH RISK RESEARCH** • **MULTIPLE SITES OR LARGE NUMBERS OF SUBJECTS** • **DOUBLE-BLIND STUDY DESIGN** • **INCLUSION OF VULNERABLE POPULATIONS** • **DEFINITIVE PHASE III TRIALS**

*Derived from information presented in Chapter 5-10 of *Institutional Review Board: Management and Function* (editors Robert Amdur and Elizabeth Bankert, 2002 edition).

During the course of the research, adverse events and other unanticipated problems which are unanticipated, at least possibly related to research participation, and suggests an increase in risk to subjects or others, must be reported to the IRB in accordance with the CU Reporting to the IRB of Unanticipated Problems policy dated January 24, 2008 (Working Practice Document #02).

At the time of continuing review or when they are submitted as modifications, interim reports from data and safety monitoring bodies, if applicable, and a summary of unanticipated problems to date will be reviewed by the IRB. The IRB may suspend or terminate research for which the risk/benefit ratio has shifted from acceptable to unacceptable due to the type, frequency, or severity of adverse events or other problems encountered during the conduct of the research.

7. Privacy and Confidentiality will be Protected

The Board will determine that there are adequate provisions to protect privacy of subjects and to maintain the confidentiality of data, where appropriate (45 CFR 46.111(a)(7); 21 CFR 56.111(a)(7)).

At the time of initial review, the IRB will ensure that each protocol includes provisions for protecting the privacy of subjects and maintaining the confidentiality of study data. The IRB will consider privacy and confidentially protections that will be in place during recruitment (e.g., by review of the recruitment plan), enrollment (e.g., by considering whether the subject being seen by others in association with the researcher could result in harm to the subject), and

participation (e.g., by examining the extent of electronic security measures to be used to protect data).

Details of where paper records will be stored, and/or how electronic data will be protected from unauthorized access, are required in the submission. In addition, consideration will be given to who has access to the data.

At times, research may involve the collection of data that is especially sensitive due to the risk of emotional, financial, legal or other harm that may be incurred if the data were disclosed outside of the context of the research. In these cases, the Board may require that a Certificate of Confidentiality, which protects against compelled disclosure and is obtained from the federal government, be obtained.

Payments to subjects for participation or reimbursement for expenses will be processed in accordance with the CU Petty Cash policy (Working Practice Document #98) to protect the confidentiality of subjects to the extent possible. When subject names will be released to institutional departments other than the IRB for the purpose of providing compensation, reimbursement, or replenishing petty cash accounts that are used for subject payments, this disclosure must be described in the consent document.

When study procedures involve audio- or videotaping, additional considerations regarding confidential storage and use of the tapes is required. See Working Practice Documents #16 and #17, Audio- and Videotaping Policy and Sample Audio-/Videotaping Addendum, respectively.

NOTE: At CU, requirements of the Privacy Standard of the federal Health Insurance and Portability and Accountability Act (HIPAA) are managed by the IRBs, which serve as the Privacy Board when such review is required, in conjunction with the efforts of the Privacy Office. The Privacy Officer acts as an agent of the IRB for processing of all HIPAA forms and approval of all forms other than waiver requests. HIPAA language is not routinely included in the consent form for the respective study, but is provided in a separate Authorization Form.

The CU policy, "CU IRB Policy on Research and the HIPAA Privacy Rule", describes the relationship of the Privacy Officer to the IRB and delineates responsibility for processing of HIPAA forms (Working Practice Document #115). Specific procedures for review of each form are described in (Working Practice Document #116, "CU IRB Procedures to Comply with Privacy Laws that affect Use and Disclosure of Protected Health Information for Research Purposes").

Additional information may also be obtained via RASCAL at the following URL: <https://www.rascal.columbia.edu/comply/hipaa.html> or from the website maintained by the Privacy Office: http://cumc.columbia.edu/hs/hipaa/policies/hipaa.html

8. Recruitment Methods and Advertising Material are Appropriate

The IRB will review proposed methods of recruitment, to ensure that the process is not affected by elements of coercion or undue influence, and that the principle of justice, as it relates to availability of innovative practices and sharing of both the burdens and risks of research, is upheld.

Acceptable recruitment methods, when patients are involved, and the treating physician is not the researcher, include:

- Treating physician introduces the study to the patient. The patient must provide written permission to allow the treating physician to forward their name and contact information to the researcher.
- Treating physician introduces the study to the patient and provides the patient with written material about the study, so that the patient may contact the researcher directly if interested in participating or learning more about the study.
- Patient obtains recruitment material from treating physician's office (e.g., waiting room) or from a public area (e.g., bulletin board) and contacts researcher directly if interested in participating or learning more about the study.

"Treating physician" refers to a clinician with whom the prospective subject has a relationship that predates introduction of the research.

When the treating physician is also the researcher, the IRB must assess whether the consent process, beginning with recruitment, may be conducted without undue influence or elements of coercion, whether due to inherent aspects of the physician-patient relationship or intentional. This is particularly important in research that presents significant risk to the prospective participant. The IRB process, beginning with the administrative review, may include requests to the researcher about how elements of coercion and undue influence may be avoided in the consent process, i.e., how the researcher will manage his/her dual roles and associated responsibilities of the fiduciary relationship vs objective scientific inquiry. Use of a witness to the consent process, assessment by a subject advocate of the patient's understanding of procedures, risks and benefits of study participation, employment of an impartial individual to conduct the consent process, and referral of the patient to an impartial physician are among the options that the IRB and researcher may consider to address concerns of undue influence or coercion.

Prior to initial approval of a protocol, and at each continuing review, the IRB will determine that plans for subject recruitment that involve advertising or other direct contact with potential subjects outside the doctor-patient relationship are consistent with the protocol, the consent form, and FDA Guidelines found in the FDA Information Sheets (the latter for those protocols to which the FDA regulations apply).

The Board, or an expedited reviewer, may review a recruitment tape (audio or video) submitted without an approvable script. If the tape follows the Board advertising review guidelines

appropriately, it may be approved. However, if there is anything in the tape that an expedited reviewer finds unacceptable, review of the tape will be referred to the full Board. At any time during the review process, the research team may be asked to submit a script so that the full Board may indicate in writing the modifications that the Board requires for approval.

Audio scripts that are for "ON HOLD" communications for phone systems or public service announcements will be reviewed by the Board or an expedited reviewer. These scripts may be approved if acceptable to the reviewer, and must be read verbatim during the recruitment process.

9. Additional Protections are in Place for Vulnerable Subjects

Prior to initial approval of a protocol, and at each continuing review, the IRB will determine that there are appropriate additional safeguards included in the study to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence e.g., children, prisoners, pregnant women, handicapped or mentally disabled persons, persons with acute or severe physical or mental illness, persons who are economically or educationally disadvantaged, or persons who are vulnerable because they are institutionalized (45 CFR 46.111(b); 21 CFR 56.111(b)).

To this end, the IRB may require that an advocate be provided, or that a Legally Authorized Representative (LAR) or Health Care Proxy (HCP), the latter under appropriate circumstances, provide permission for enrollment, in addition to consent or assent from the subject, when the capacity of the prospective subject to provide legally effective consent is in question. Procedures for determining capacity must be described by the investigators when individuals who may lack capacity to consent will be considered for enrollment. If the study population involves individuals who are likely to have diminished capacity to provide consent during the course of their participation, procedures for periodically assessing capacity, and implementing measures to provide appropriate protection measures throughout the study should also be included. These may include execution of a Health Care Proxy at the time of enrollment, procedures for ending participation when the individual can no longer make competent decisions, or involvement of a study partner who is authorized to provide information about the subject.

In any situation, but particularly when a prospective subject is subordinate to a researcher (e.g., patient, student, employee), the IRB may observe the consent process or require changes in recruitment procedures to eliminate or reduce elements of coercion or undue influence.

When children will be enrolled, the requirements of Subpart D of 45 CFR 46 and 21 CFR 50 will be considered. Assent will be obtained when deemed appropriate by the Board, and parental permission will be sought, unless waiver criteria stipulated in the federal regulations are met. Permission of one parent is generally sufficient, however, the permission of both parents will be required (with the qualifiers identified in Subpart D) for research that is greater than minimal risk but does not offer the prospect of direct benefit for individual subjects. If wards will be enrolled in such research, an independent advocate will be identified for each subject; it may be acceptable for one advocate to represent more than one child.

The requirements of Subparts B and C of 45 CFR 46 will be considered for all research that involves pregnant women or prisoners, respectively, and the reviewing IRB will make all necessary determinations.

Additional information about the review of research involving vulnerable subjects may be found in Section VI.D., Review of Specific Types of Research.

10. Potential Conflict of Interest of Investigators is Eliminated, Mitigated or Managed

Annual and protocol-specific conflict of interest forms are reviewed through a process that involves individual evaluation of positive responses ("anomalies") by staff from the Office of Research Compliance and Training (ORCT).

Protocol-specific COI disclosures for all key personnel of the research team named on IRB protocols are submitted electronically in RASCAL and reviewed by ORCT. If there is a positive anomaly on a protocol-specific disclosure, then the electronic submission system flags the study as positive for COI and prohibits the IRB Chair/Member from the ability to approve the study, until the flag is cleared by ORCT. The majority of COI reviews are conducted through this process.

- Notification of the outcome of this review for anomalies that do not meet the University threshold to be considered a significant financial interest is provided to the IRB for consideration during its review.
- Procedures are in place to refer conflicts that meet or exceed the University threshold for significant financial interests to the institutional Conflict of Interest Committee. The Committee is comprised of faculty and representatives from administrative units within the University that have responsibility for research functions, and serves to eliminate, mitigate, or manage significant financial conflicts of interest. Notification of Committee action for conflicts that required full Committee review and involve human subjects research is provided to the IRB for consideration during its review of the research.

The University threshold for a significant financial interest is defined in the 'University Policy on Financial Conflicts of Interest in Research' adopted on April 3, 2009 and effective July 1, 2009. The Policy is posted on the website of the Executive Vice President for Research at http://evpr.columbia.edu/content/selected-policies."

The IRB is notified of the outcome of the administrative or Committee review, as applicable, by attachment within RASCAL of the disclosure form and accompanying notes to the relevant protocol. The documentation includes the responses from the disclosure form, indicates whether the financial interest was considered significant or nonsignificant in relation to the University COI policy, and describes any actions taken to eliminate or mitigate the conflict of interest. Such actions may include reduction of a significant interest to a nonsignificant level, change in roles for the individual(s) with the conflict, or departure from the research team of the individual(s)

with the conflict. The IRB has the authority to impose any requirements it deems appropriate, regardless of the outcome of the review by the ORCT, and COI Committee (if applicable), although the IRB may not overturn decisions made by either entity.

Additionally, the IRB may forward COI concerns to ORCT or the COI Committee, beyond those that may be received by ORCT through the electronic submission system. If, during its review, the IRB identifies a financial interest that was not disclosed on the Protocol-Specific disclosure form, and therefore did not undergo review by the ORCT, the issue will be referred to that office for review as a result. The referral will be documented in the relevant IRB meeting minutes, if the IRB review was at a convened meeting, If the IRB review was an expedited process, or the protocol qualified for exemption, the referral will be documented in the RASCAL Notes for the specific protocol. The usual process for review of anomalies would then commence, with review by the COI Committee if warranted, and attachment of a summary resolution form in RASCAL. Final approval by the IRB will not be granted until the COI Committee review(s) are complete, the IRB has had an opportunity to review the outcome, and the IRB is either satisfied with the COI Committee requirements or implements additional requirements (e.g., consent form disclosure).

Annual disclosures of financial interest that are not protocol-specific are also required, for all individuals listed on IRB submissions. Instructions for the annual disclosure forms state that a new disclosure form must be filed whenever changes to the individual's or his/her family's financial portfolio change such that a response on the disclosure form must be modified.

C. IRB Review of Specific Events

1. Initial Review (Review of a New Protocol)

The term "initial review" as used in this section refers to the review of a new protocol until such time as it is approved, i.e., if several reviews by the convened Board or expedited reviewer were necessary prior to approval, all would be considered part of the initial review.

The Boards follow HHS and FDA regulations concerning institutional review boards and the requirements of these written procedures for conducting their initial review of research and for reporting their findings and actions to the investigator, and when applicable, to the institution (45 CFR 46.108; 46.103(b)(4); 46.103(b)(5); 21 CFR 56.108 (a)(1)).

Each Board will determine that the requirements identified in Section B, IRB Criteria for Review, are satisfied before they approve research.

In addition, the Boards will ensure that all applicable approvals, confirmations or review, as applicable, from internal and external committees have been obtained. These include, but are not limited to, the Herbert Irving Comprehensive Cancer Center Protocol and Research Monitoring Committee (PRMC), the Institutional Biosafety Committee (IBC), the Joint Radiation Safety Committee (JRSC), the Radioactive Drug Research Committee (RDRC) (all internal), and the Recombinant DNA Advisory Committee (RAC) (external).

If a protocol is in any way cancer-related, review by the IRB may not proceed until approval from the Cancer Center Protocol Monitoring and Review Committee (PRMC) is obtained (Working Practice Documents #6 and 7). IRB review may proceed while other approvals or confirmations are in progress, insofar as the information that will be obtained from the respective approval or confirmation is not needed to conduct the IRB review.

Compliance with institutional policies or requirements such as qualifications of PIs (Working Practice Document #13), submission to Medicare for approval to bill for allowable items relative to Category A or B devices (see Working Practice Document #162), and training requirements for research staff (see Section X of these written procedures) will also be verified during the initial review.

The expiration date of IRB approval is the last date on which the study can be conducted under the respective IRB approval. Expiration date for new protocols and renewals is calculated electronically in RASCAL as follows:

a. for full Board reviews, by adding one year to the date of the last convened meeting at which the submission was discussed, and subtracting one day;
b. for expedited reviews, by adding one year to the date on which the submission was approved, and subtracting one day;
c. for exempt reviews, by adding two years to the date on which the submission was approved, and subtracting one day.

IRB staff may revise the expiration date when preparing minutes. Such action would be necessary when:

a. The IRB specifies an approval period of less than one year;
b. A submission is approved via a facilitated review process when CU is not the IRB of record, and the official expiration date is the one determined by the IRB of record;
c. A modification is approved for a protocol that was formerly determined to be exempt, but no longer meets the exemption criteria due to the nature of the modification.

When a modification is approved, the expiration date of IRB approval for the protocol, which was calculated at the most recent review of the entire protocol (e.g., initial review or continuing review), is retained.

2. Review of Modifications

Regulations require, and Columbia policy reiterates, that any change to any approved non-exempt protocol must be submitted to the IRB for prospective review prior to implementation, except when a change is necessary to eliminate an immediate hazard to subjects and there is not sufficient time for IRB review before the change must be implemented. A change may relate to any aspect of the study, e.g., personnel, study procedures, consent documents, recruitment

material, sponsor's protocol, study instruments. Changes are commonly referred to as modifications at Columbia, although technically they may be additions or deletions.

When a change is proposed for a study that requires full Board review, the modification must also be reviewed by the convened Board, if the change is substantive. The regulations do not define what is meant by a substantive change; therefore, a guidance document has been prepared for use by Columbia investigators that identifies types of changes that are likely to be considered substantive (see Working Practice Document #112). Substantive changes are those that affect one or more of the regulatory criteria for approval. The approval date for modifications that require full Board review will be either: a) the date of the meeting at which the convened IRB reviewed and approved the modification, if the IRB did not require any revisions; or b) the date that the IRB Chair or other experienced IRB member approved the modification after the revisions stipulated by the IRB at the convened meeting were reviewed and found to be adequate. Non-substantive changes (to a study that, in its entirety, requires full Board review) may be reviewed by expedited review, in accordance with the expedited review categories defined by FDA and DHHS (63 FR 60364-60367, November 9, 1998).

Changes proposed for studies that are eligible for expedited review may also be reviewed by expedited review, unless the change causes the protocol to be ineligible for expedited review (e.g., increases risk level to greater than minimal, adds procedures that do not fall into any of the expedited review categories).

The Chair has the prerogative to route any modification to the full Board for review, regardless of whether it is eligible for expedited review per the federal statutes.

The Boards must ensure that the IRB review criteria articulated in 45 CFR 46.111 and 21 CFR 56.111, as applicable, are met for the protocol prior to approving a modification to an existing protocol. Local requirements such as review by the Cancer Center PRMC, IBC signoff, Radiation Safety review, and training requirements must also be satisfied.

When a modification includes new information related to risks, additional or modified procedures, or other factors that may affect subjects' willingness to continue participation, the IRB must consider options for providing this information to participants. These may include obtaining signatures on a revised consent form, providing an information sheet to participants, or verbally informing subjects by telephone or in person. Regardless of the method selected, content of the documents or scripts that will be used should be provided to the IRB for review, and means of documenting notification to the subjects should be specified.

Changes in approved research initiated without IRB approval, whether to eliminate an immediate hazard to subjects when there is not sufficient time for IRB review before the change must be implemented, or that have been discovered to have occurred for other reasons (i.e., protocol violation), have to be:

- Promptly reported to the IRB.
- Reviewed by the IRB to determine whether the change is consistent with ensuring the subjects' continued welfare.

3. Review of Reports of Unanticipated Problems involving Risks to Subjects or Others

Submission of reports of unanticipated problems including adverse events will be in accordance with the CU Reporting to the IRB of Unanticipated Problems Policy (Working Practice Document #02).

Reports of unanticipated problems that meet the criteria for individual submission at the time of occurrence will be presented for discussion at a convened meeting of the IRB after review by a primary reviewer. The Board will determine whether the report is complete or additional information is required. In addition, a determination will be made of whether the protocol and/or consent document(s) should be revised, if this is necessary as a result of the UP and has not already been initiated by the study team. Finally, the Board may impose restrictions on the research (e.g., more frequent reporting, suspension of enrollment, suspension of the study, termination, etc.) if review of unanticipated problem reports results in a determination that the risk/benefit ratio has become less favorable, or require notification of current subjects when such information may relate to subjects' willingness to continue to take part in the research.

Particular attention will be focused on reports of unanticipated problems that occur at a Columbia site in an investigator–initiated protocol for which there is no other monitoring outside of the research team.

The Board may take action appropriate for the circumstances to protect the safety, welfare and rights of research subjects. Investigators are encouraged to report any trends to the Board.

4. Review of Reports of Protocol Deviations or Violations

Definitions of "deviation" and "violation" may be found in Section V.B.6. of these written procedures.

Both protocol deviations and violations occur when there is a discrepancy between the protocol and the activities being performed within the study. While either one may or may not increase risk to subjects, it is particularly important that the IRB be notified immediately when the deviation or violation could potentially cause increased risk to subjects or the study as a whole.

Protocol violations can be categorized as either minor or major, and may or may not affect individual subjects. Major deviations or violations should be reported immediately to provide an opportunity for the IRB to assess whether the study should continue, and whether changes to study procedures are required.

a. Major protocol violation:

   1) The violation posed a significant risk of substantive harm to the individual research subject;

2) The violation has compromised the scientific integrity of the data collected for the study;

3) There is evidence of willful or knowing misconduct on the part of the investigator(s) and/or study staff,

4) There is other serious or continuing noncompliance with federal, state or local research regulations.

b. Minor protocol violations:

1) The violation has no substantive effect on the risks or benefits to the individual research subject(s);

2) The violation has no substantive effect on the data collected;

3) The violation was not the product of willful or knowing misconduct on the part of the investigator(s) or study staff;

4) There is no serious or continuing noncompliance with federal, state or local research regulations.

Major protocol violations should be submitted through the Unanticipated Problems Report Module in RASCAL if the violation resulted in a potential increase in the risk or harm to subjects, or involves a misadministration of drug or therapy. Any misadministration of drug or therapy (whether an increase or decrease in prescribed dose) should also be reported to the IRB COT to ensure reporting to federal regulatory agencies, as appropriate. All other protocol deviations/violations should be submitted through the Modification module in RASCAL.

The IRB will review protocol deviations and modifications to determine whether the risk/benefit ratio of the protocol has increased as a result of the deviation. Potential or real harm to the subject will be assessed. A corrective plan should be submitted by the researcher with the protocol deviation and will be reviewed by the IRB to ensure that adequate steps are being taken to avoid recurrence of the deviation. In some cases, referral to the COT for initiation of a noncompliance inquiry may be required, if the situation meets the reporting criteria for serious or continuing noncompliance.

5. Review of Emergency Use Requests

Emergency use is defined by the FDA as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)). This does not include the "off-label" uses of approved medical products in the practice of medicine (i.e., not in a research context). Such uses are not considered research, but rather the practice of medicine for the treatment of patients with non-FDA-approved products. The data from such uses may not be used for research purposes.

Emergency use requests are processed by IRB staff (ED, AD, or a Manager of an IRB) as review by appointed IRB members or the convened Board is not required. When staff are asked to provide documentation that the IRB office is aware of an emergency use request so that the investigational product may be shipped, they do not review the procedures for use of the product. Rather, they ensure that the regulatory criteria for emergency use are met including provisions for obtaining informed consent or waiver under appropriate circumstances, and the need for all required information to be provided to the IRB within 5 days of use of the test article.

In general, emergency use of an investigational agent may only be authorized once. If future need for use of the test article under similar circumstances is anticipated, a full protocol should be submitted to the IRB for review.

Refer to section VI.D.10 for provisions regarding emergency research.

a. Initial Notification to the IRB

Emergency use of a test article under the conditions specified in 21 CFR 56.102(d), 21 CFR 56.104, and 21 CFR 312.36 does not require prospective IRB review. However, written IRB acknowledgment of notification by a clinician of the proposed emergency use of a test article, and receipt of a consent document, if available, may be required by the manufacturer of the product to permit shipment of the investigational product to the institution.

When the IRB office is notified of proposed emergency use of an investigational agent, a letter will be provided to the investigator from the IRB acknowledging the proposed use and advising the clinician of the need for a follow-up report to the IRB within 5 days, if all required information was not provided in the emergency use request. See Working Practice Document #99 for a sample letter of acknowledgment. Notification to the IRB also provides the mechanism for the institution to monitor such emergency use situations.

Consent for emergency use of an investigational agent should be prospectively obtained when possible. In these cases, the consent process, plans for obtaining assent, where applicable, and consent documents should be included in the materials submitted to the IRB with the request for emergency use. Waiver of informed consent in conjunction with emergency use is discussed under Informed Consent below.

b. Consent Requirements for Emergency Use of a Test Article

If the use involves the individual emergency administration of an FDA regulated article under 21 CFR Parts 50 and 56, the requirement for prior consent may appropriately be waived, as provided for in 21 CFR 50.23 (a)-(c), 56.104(c), 56.102(d), and these written procedures. The IRB will acknowledge rather than approve the waiver.

The obtaining of informed consent shall be deemed feasible unless, before use of the test article (except as provided below), both the treating physician and another physician who is not otherwise involved in the use of the investigational product certify in writing all of the following:

1) the patient is confronted by a life-threatening situation necessitating the use of the test article;
2) informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally effective consent from, the patient;
3) time is not sufficient to obtain consent from the patient's legal representative; and
4) there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the patient.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the patient, and time is not sufficient to obtain the independent determination required in the above paragraph of this section in advance of using the test article, the determinations of the clinician shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the care of the patient.

The documentation described in this section and required per FDA regulation shall be submitted to the IRB within 5 working days of the use of the test article, if it was not provided with the emergency use request.

c. Documentation Required

Within 5 working days of the emergency use of an investigational product, the physician responsible for the use must provide the following information to the IRB:

1) an explanation of the life-threatening situation necessitating the use of the test article and the patient's initials;
2) description of the investigational product, including name or other unique identifier, and IND, BB-IND, or IDE number, as applicable;
3) a copy of the consent document that will be/was used or an explanation of why it will not be or was not possible to obtain informed consent (i.e., details in item b above); also, if the patient was a child, whether assent of the child will be/was obtained;
4) concurrence from another physician who is not otherwise involved in the use of the investigational product that the situation is/was life-threatening and that no alternative standard treatment is/was available;
5) an indication of whether additional uses are anticipated, in which case a protocol and consent form must be submitted for Board approval.

The documentation, whether received with the request for emergency use or within 5 days of use of the test article, will be reviewed by the IRB Executive Director, Associate Director, or one of the IRB Managers to assess compliance with the regulations and CU policy for emergency use

and, when applicable, the consent form waiver. Consultation from a physician who is a member of the IRB will be sought as needed to make the required determinations.

If a protocol for additional uses is submitted, the Board will prospectively review, at a convened Board meeting, proposals for the treatment (FDA 21 CFR 312.34 and 312.35) or compassionate use of the test article under applicable FDA regulations and in accordance with the review of protocols involving investigational products as described in these written procedures. Data collected from these activities, when the proposed activities have been reviewed by the convened Board, may be used for research purposes.

6. Facilitative Review

Facilitative review will occur when CU is relying upon the review of another IRB, in accordance with the terms of an IRB Authorization Agreement. The type of reviewer and extent of review required is dependent upon the specific Agreement, as described in Working Practice Document #05.

IRB Authorization Agreements to which Columbia is a party and which apply to multiple projects are updated as necessary and are kept on file in the IRB office. Periodic meetings are held between representatives of the CU IRB Office and the IRB of each institution with which an Agreement exists. The purpose of these meetings is three-fold: a) to ensure that procedures remain appropriate; b) to discuss whether the respective Agreement requires updating or should be dissolved; and c) to keep abreast of the IRB processes and institutional research perspectives of each institution.

7. Continuing Review

All non-exempt human subjects research for which there are plans to continue beyond the expiration of the current IRB approval must be re-reviewed and approved by the IRB for an additional period. Continuing review may stop only when the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and collection and analysis of private identifiable information has completed.

The Board will determine whether all regulatory and institutional criteria have been met during the conduct of the research to date. While the focus of the initial review is to determine whether the risk/benefit ratio of the proposed research is acceptable, plans have been developed to minimize risk, and informed consent procedures are appropriate, the focus of the continuing review is to provide oversight and to evaluate, to the extent possible, whether the actual risk/benefit ratio is still considered to be acceptable, and to assess the conduct of the research activities to date.

Continuing review should occur within the 60 days prior to the study's expiration date. Review of a change in the study does not routinely alter the date by which continuing review must occur. However, if a modification is submitted that requires review of all study procedures and

documents, to the extent that all information required for consideration of renewal is requested and found to be acceptable, the Board may consider review of the modification to be equivalent to a continuing review and recalculate the expiration date for IRB approval of the protocol. In these situations, it will be documented in the IRB record that all requirements for continuing review, in addition to those related to the modification, were met.

Each Board has authority to determine, at their discretion during the continuing review process, which research activities need verification, from sources other than the investigator, that no material changes in the research have occurred since the previous IRB review. To determine which projects need verification, the Board will consider such things as an unexplained and sudden increase in risk to subjects, FDA audits, site visits conducted by authorized personnel, reports from "whistleblowers," etc (45 CFR 46.103(b)(4); (FDA 21 CFR 56.108(a)(2)). Verification may be obtained through contact with the sponsor, FDA, or cooperative group, as applicable, (e.g., to verify protocol version dates), by audit of the investigator's files, and via requests for information from a coordinating center or monitoring board.

When initial review was conducted by an expedited review procedure, continuing review will usually be conducted via an expedited process, provided all study procedures continue to fall within one or more of the federal categories of expedited review. For protocols reviewed via expedited review, the approval period is usually one year, because protocols that are eligible for expedited review do not generally present the safety concerns which would warrant review more frequently.

For studies approved under expedited procedures, continuing review must occur within one year of the date of expedited approval by the IRB Chair or designee.

When initial review was conducted by a convened meeting of the IRB, and the procedures have not substantively changed, continuing review will also be conducted at a convened meeting (45 CFR 46.108(b); 46.109(e)), with the exception of the limited circumstances described by expedited review categories (8) and (9). (See List of Expedited Review categories, Appendix IX.) If study procedures have evolved, whether through modifications or completion of active intervention, such that all remaining procedures meet the criteria for one or more of the expedited review categories, continuing review may be conducted via an expedited review process.

For full Board reviews, the maximum approval interval shall be one year from the date of the convened meeting at which the study was approved, either unconditionally (i.e., "approved") or with specific conditions which the IRB Chair or his/her designee can verify, i.e., "deferred to Chair" status.

There are times when a renewal can be approved for enrolled subjects (or another subset of the study population), but not for enrollment, or perhaps excluding a particular subset, until specific IRB requirements are satisfied. In these situations, the Board (for full Board reviews), Chair or other reviewer (for those submissions eligible for expedited review), may approve the protocol, to avoid a lapse in approval. If the IRB determines that it is important to add the excluded procedures or subject group, the approval may include a requirement that the remaining elements

be added and the entire project reviewed by a specific time within the coming year, i.e., designate an approval period of less than one year.

Each Board has authority to suspend or terminate the approval of research that is not being conducted in accordance with federal regulations or in accordance with stipulations imposed on the research activity by the IRB. This may occur at the time of continuing review, or at any other time after initial approval of the research.

IRB Review Criteria as articulated in 45 CFR 46.111 and 21 CFR 56.111 must be satisfied before any non-exempt event that is submitted for review and approval (e.g., new protocol, renewal, modification) may by approved. If a Board, during a full Board review, determines that the review criteria are no longer met, study activities may be suspended or the study may be terminated, as appropriate to the reason by which the review criteria cannot be met. Similar situations encountered during an expedited review of a modification will be brought to the Board for discussion although the Chair may suspend study activities prior to the Board review, if warranted to ensure subject safety or the integrity of the research.

Any suspension or IRB-initiated for-cause terminations which occur during continuing review will be reported promptly to the investigator, and to the ED, the AD, and COT, who will inform the appropriate IO. The ED will notify the FDA, if applicable, and OHRP of the suspension or termination (45 CFR 46.108(a); 21 CFR 56.113). If suspension or termination occurs at the time of continuing review, the IRB, in consultation with the researcher or other appropriate individuals, will determine the appropriate procedures for discontinuing study procedures with enrolled subjects. Safety of subjects will be the primary concern.

Modifications to approved research may be considered by the IRB during continuing review, and must be approved prior to implementation. When a modification is submitted in conjunction with a renewal request, the Board may approve both or approve the renewal without the modification.

When a modification includes new information related to risks, additional or modified procedures, or other factors that may affect subjects' willingness to continue participation, the IRB must consider options for providing this information to participants. These may include obtaining signatures on a revised consent form, providing an information sheet to participants, or verbally informing subjects by telephone or in person. Regardless of the method selected, content of the documents or scripts that will be used should be provided to the IRB for review, and means of documenting notification to the subjects should be specified.

Further explanation of how continuing review serves an important function in oversight monitoring is provided in Section IX.A.

a. Continuation Past Expiration of IRB Approval

Applicable regulations require that each non-exempt protocol be reviewed at least annually. The IRB cannot extend a study's approval beyond the expiration date without conducting a review,

but must consider various factors when addressing active studies for which there may be a lapse in IRB approval:

1) Where the IRB does not re-approve a research study by the specified IRB expiration date, subject accrual may not occur and all study-related procedures must cease pending re-approval of the research by the IRB. Study-related procedures include recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information.
2) Where failure to continue study procedures would seriously and adversely affect the safety or well-being of enrolled subjects, the IRB Chair may review these studies on an individual basis prior to substantive review of the protocol by the convened Board or designated reviewer (as applicable to the level of review required). The purpose of the Chair review is to assess whether he/she concurs with the PI that there exists the potential for harm to subject(s) as a result of interruption of study procedures.

   Continuation of research activities for currently enrolled subjects may be permitted when the IRB Chair finds that it is in the best interest of the individual subjects to do so and the PI is actively pursuing renewal of the study protocol. When an IRB Chair elects this option, the approval to allow currently enrolled subjects to continue study treatment must be documented in writing and effective for a finite period that allows opportunity to complete the IRB review.
3) When continuing review of a research protocol does not occur prior to the end of the IRB approval period, IRB approval expires automatically. This expiration will not be reported to OHRP as a suspension of IRB approval under HHS regulations, in accordance with HHS guidance.

b. Procedures for Determining Which Projects Require Review More Often Than Annually

For each approval, the IRB will determine the interval for which approval should be granted, appropriate to the vulnerability of subjects, experience of the investigator, degree of risk to which subjects are exposed and other information provided for the initial or continuing review of study. In no case will the IRB grant approval for a period that is greater than one calendar year.

These considerations for the length of approval time will be made at the time of motion for approval of a study during the IRB meeting, for projects that require full Board review. When any of the following (non-inclusive) situations exist, the Board will consider an approval period of less than one year:

1) the need for increased monitoring to evaluate anticipated risks;
2) scant safety data due to early introduction of a test article in clinical studies (e.g., early Phase I studies);
3) the need for increased monitoring to evaluate potential noncompliance or for projects conducted by investigators who have previously failed to satisfy IRB requirements.

8. Review of Termination Requests

Requests by researchers for closure of an approved project are reviewed by a primary reviewer prior to presentation at a convened meeting. The Board reviewer will have access to the staff reviewer's notes, and will evaluate information provided about number of subjects enrolled, unanticipated problems, and study results to determine whether closure is appropriate, and to ensure that all outstanding issues have been adequately addressed.

If follow-up of participants for safety reasons is permitted or required by the IRB, participants should be so informed, and any unanticipated problems or adverse outcomes should be reported to the IRB. In these cases, IRB approval should remain current.

9. Suspension and IRB-initiated For-cause Termination of Research

Each Board has authority to suspend or terminate the approval of research that is not being conducted in accordance with federal regulations, state law, or institutional policy, has been associated with unexpected serious harm to subjects, has an unfavorable risk/benefit ratio, or is not being conducted in accordance with stipulations previously imposed on the research activity by the IRB Board.

A suspension is a directive of the convened IRB or other authorized individual to temporarily stop some or all previously approved research activities short of permanently stopping all previously approved research activities. Suspended protocols remain open and require continuing review.

A termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research protocol. Terminated protocols are considered closed and no longer require continuing review.

The ED, AD (in the absence of the ED), or an IRB Chair may unilaterally suspend a study if he/she receives information that requires the immediate action for the protection of human subjects or to address a concern regarding potential noncompliance with federal, state, or institutional regulations/policies; such actions should occur when, in the judgment of the ED, AD (in the absence of the ED), or IRB Chair, it would be inappropriate to wait until the next meeting of the IRB or Executive Committee of the IRB.

When study approval is suspended or terminated, the convened IRB, or the individuals making the determination, consider the following:

- Actions to protect the rights and welfare of currently enrolled subjects.
- Whether any adverse events or outcomes have been reported to the IRB.
- Whether current subjects must be informed of the termination or suspension, and if so, in what manner.

- Whether procedures for withdrawal of enrolled subjects take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another investigator, or continuation in the research under independent monitoring).

Any suspension or for-cause termination of IRB approval will be reported promptly to the investigator and, if the action was initiated by the Chair, the ED, the AD, and COT, who will notify the appropriate IOs, the FDA (Director, Division of Biomedical Monitoring, Office of Compliance, Center for Devices and Radiological Health, for device research; Branch Chief, Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research, for drug research), if applicable, and OHRP (Division of Compliance Oversight) of the suspension or termination (45 CFR 46.108(a);(21 CFR 56.113). If the action was initiated by the ED or AD, the Chair of the reviewing IRB will also be notified of the action.

Although there is no regulatory authority for appeal of Board decisions in suspending or terminating approval of research, the PI may reply in writing to suspension or determination decisions, and have the response considered by the Board.

D. Review of Specific Types of Research

1. Review of Research involving Investigational Drugs

For studies involving investigational drugs, or approved drugs used off-label, IRB staff will perform the following functions during the pre-review process:

a. Determine whether the regulatory status of the drug as used in the proposed research is clearly indicated in the materials submitted for Board review, with appropriate FDA documentation if necessary.

b. If the regulatory status is not clear, staff will request one of the following from the investigator or sponsor:

    1) A letter from FDA that documents the status, and if an IND is required, a letter from FDA that documents the approval of the IND;

    2) A copy of the sponsor's protocol or Investigator's Brochure that reflects the IND number (for drugs that are not approved by the FDA) or a copy of the package insert (for drugs that are FDA-approved);

    3) Other appropriate documentation of the need for an IND or exemption thereof.

During its review of the proposed research, the IRB will consider, in addition to the review criteria previously described that applies to all reviews:

a. Whether an IND is required, if one has not been obtained;

b. Whether the investigational drug is being dispensed in accordance with the NYP Investigational Drug Policy (Working Practice Document #18) and Research Pharmacy policies, as applicable;

c. Whether specific information regarding birth control measures must be provided to subjects with reproductive capacity;

d. Whether special handling is required by research staff, subjects, or others.

2. Review of Research involving Medical Devices

For studies involving medical devices, IRB staff will perform the following functions:

a. Determine whether the regulatory status of the device is clearly indicated in the materials submitted for Board review, and if an IDE is required, a letter from FDA that documents the approval of the IDE..

b. If the regulatory status of the device is not clear, staff will request one of the following from the investigator or sponsor:

   1) A letter from the sponsor stating and explaining why the device is non-significant risk (NSR); or

   2) If the device is a Significant Risk (SR) Device, a letter from the FDA approving the Investigational Device Exemption (IDE) and providing the IDE Number or IDE Supplement Number, a letter from the sponsor providing the IDE number, or a revised protocol from the sponsor that includes the IDE number; or

   3) Other written documentation that sufficiently establishes the regulatory status of the device, which may include a statement by the sponsor that the device is not of a regulatory status for which individual written FDA documentation exists, or a letter from the FDA declining to issue an IDE number, stating it was not necessary; for device studies that meet the exempt criteria in 21 CFR 812.2, and which may not have been submitted to FDA, the investigator should justify how the exemption criteria are met.

c. Ensure that a trial involving a device which has been identified as requiring authorization for billing to Medicare receives such authorization before subjects are enrolled. Procedures described in Working Practice Document #162, which addresses notification to the Office for Billing Compliance and CTO of a device study for which such procedures apply, will be followed.

d. Ensure that plans are in place for appropriate handling, storage, and disposition of the devices.

The Board acts in accordance with the following reference information regarding medical device approval when reviewing a protocol that involves an investigational device.

a. Research involving a medical device for human use that qualifies as an NSR Device (unless the device is banned), may begin upon approval by an IRB and does not require the issuance of an Investigational Device Exemption (IDE) by the FDA (21 CFR 812.2 (b)(1)).

b. Research involving a medical device for human use that does not qualify as an NSR device and is not exempt is classified as a Significant Risk (SR) Device. Research involving SR devices (unless the device is banned) cannot begin until the FDA issues an IDE and approval is granted by an IRB (21 CFR 812.30 (a)).

A significant risk device is an investigational device that meets any of the following criteria (21 CFR 812.3(m)):

a. is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

b. is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

c. is for a use of substantial importance in diagnosis, curing, mitigating, or treating disease, or otherwise preventing impairment of human health, and presents a potential for serious risk to the health, safety, or welfare of a subject; or

d. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Before approving research involving a medical device for human use, the Board will determine if the device is a SR Device, an NSR Device, or whether the research use of the device is exempt from the IDE regulations.

a. If the Board determines that the device is NSR, the Board may proceed to review the research activities and investigator under its normal procedures for reviewing research projects.

b. If the FDA has issued an Investigational Device Exemption (IDE) for the proposed use of the device, then it is, in most cases, considered to be an SR device.

c. If the FDA has not issued an IDE for the proposed use of the device, then the Board shall consider the following elements in determining whether the device is SR or NSR:

    1) An explanation provided by the sponsor of why the device is not a significant risk device; and

    2) Whether the use of the device might cause harm to any of the subjects, and the nature of the harm that may result from use of the device.

    Note: If the subject must undergo a medical procedure as a part of the study, and that medical procedure is not one which the subject would otherwise undergo as part of standard medical care, the Board must consider the risks associated with the procedure as well as the use of the device. If potential harm to subjects could be life-threatening, could result in permanent impairment of body function, or permanent damage to body structure, the device should be considered SR.

d. If the Board determines the device is SR, and there is no IDE assigned, it will provide the investigator and, if appropriate, the sponsor, with its finding. The sponsor is responsible for notifying the FDA of the Board's SR determination.

   The Board will not review the research until the sponsor provides proof that the FDA has granted an IDE to the sponsor. If the FDA has not responded to the IDE application, as described in 21 CFR 812.30, this proof may consist of a letter showing that an IDE application was submitted at least 30 days prior to the date on which the Board reviews the research and the FDA has not issued a hold on use of the device.

e. If the Board determines that the investigation meets one of the IDE exemptions listed at 21 CFR 812.2(c), this finding will be noted in the minutes, and the Board will not make an SR/NSR determination. Also, if the investigation involves a device that is cleared for marketing through the PMA process, and the device is being studied for the purpose(s) for which the device is labeled, the Board will consider the investigation exempt from the IDE regulations. This finding will be noted in the minutes, and the Board will not make an SR/NSR determination.

In those infrequent instances when a medical device study is approved under expedited review procedures (category 1.b.), documentation of required findings by the Board reviewer would be entered in the IRB record, e.g., Notes section of RASCAL.

3. Review of Humanitarian Use Devices

Humanitarian Use Devices (HUDs) are intended to benefit subjects in the treatment or diagnosis of diseases or conditions that affect or manifest in fewer than 4,000 individuals in the United States per year. HUDs are considered by the FDA to be approved for marketing.

The degree of safety and efficacy testing required for FDA approval of an HUD is less than that required for other medical devices, because more rigorous testing prior to marketing is not feasible for devices that affect a relatively small subset of the population. Therefore, IRB review is required for these approved devices because safety and efficacy data will be collected while it is marketed.

Two general situations exist for which a protocol that utilizes an HUD is submitted to the IRB:

- Where the HUD will be used as described and for the indication approved in the HDE;
- Where the HUD will be used in a manner, for an indication, or in a population other than that approved in the HDE.

The former does not constitute research, while the latter does.

All protocols involving HUDs will be reviewed at a convened meeting of the full Board at both the initial and continuing reviews.

a. Use in Accordance with the HDE

IRB review of HUDs is required under federal regulation (21 CFR 814). During review of the proposed use of the HUD, the Board must:

1) determine that the FDA has granted a Humanitarian Device Exemption (HDE) to the sponsor.

2). determine that the investigator intends to use the HUD according to its FDA approved use.

After the Board has determined that the FDA has granted an HDE, the Board may proceed to review the proposed activities and investigator in consideration of the IRB review criteria described in 45 CFR 46.111, with the exception of the requirement for informed consent. Informed consent is not required for use of an HUD in accordance with its FDA approved indication. However, the Board may require consent in such instances at its discretion.

b. Use Not in Accordance with the HDE

When use of an HUD for research is proposed, the IRB should consider all factors relevant to use of an investigational device, as well as the IRB review criteria defined in 45 CFR 46.111.The Board will require informed consent for any research use of the HUD (i.e., outside of the FDA-approved indications) of an HUD.

4. Review of Research involving Pregnant Women, Neonates, and Fetuses (45 CFR 46, Subpart B)

Pregnant women, fetuses, and neonates are a vulnerable population and, as such, require additional protections when they are research subjects. It is recognized, however, that pregnant women, fetuses, and neonates should not be denied the benefits of participating in research. Distinction must be made between studies for which the reproductive status of the pregnant woman or the unique characteristics of fetuses and neonates are criteria for inclusion in the research, and studies for which the pregnancy status of the woman is incidental. In regards to the latter, Subpart B requirements need not be met although in all cases, risks specific to pregnant women, neonates, or fetuses should be addressed during the consent process.

When the Boards consider research which requires the involvement pregnant women, neonates, or fetuses, they will ensure that all requirements of 45 CFR 46 Subpart B are met prior to approval of the research.

In addition to applying the criteria for IRB review identified in 45 CFR 46.111, they will ensure that:

a. there is adequate expertise on the Board to evaluate the risks and benefits related to the inclusion of pregnant women, fetuses and neonates, engaging consultants where necessary;

b. the determinations required by Subpart B are documented appropriately in the IRB record;

c. the proposed involvement of pregnant women or fetuses meets all requirements for inclusion as stated in 45 CFR 46.204;

d. the proposed involvement of neonates meets all requirements for inclusion as stated in 45 CFR 46.205;

e. proposals for which the inclusion of pregnant women, neonates, or fetuses is not approvable per Subpart B will be referred to the HHS Secretary for review;

f. informed consent is obtained per provisions of Subpart B for pregnant women who have reached the age of majority or are legally emancipated;

g. informed consent is obtained per provisions of Subparts B and D for pregnant minors (where research is related to prenatal care, consent of the pregnant minor may be acceptable);

h. consent documents contain information regarding risks of breastfeeding, when risks to the pregnant woman or neonate is determined to be greater than minimal;

i. consideration is given to excluding pregnant women when the woman's reproductive status is not relevant to the research and risks to the pregnant woman or fetus is determined to be greater than minimal.

CU has developed guidance (Working Practice Document # 103) for obtaining consent from women during labor, in acknowledgement of the fact that some research can only be done during this period, it may not be possible in some circumstances to obtain consent before labor begins, and women who are capable of providing consent during labor and wish to participate in research should be able to do so.

Proposed informed consent procedures for pregnant women who are not in labor will be reviewed in consideration of the general requirements for informed consent, with special attention to the explanation of potential risks and benefits to both the woman and fetus.

5. Review of Research involving Prisoners (45 CFR 46, Subpart C)

The purpose of this section is to provide guidelines for review that will ensure additional safeguards for the protection of prisoners involved in research. Prisoners may be under constraints because of their incarceration, which could affect their ability to make a truly voluntary and non-coerced decision whether or not to participate as subjects in research.

Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

An IRB Chair may elect to review protocols that include populations with an increased risk of incarceration as prisoner protocols, even if the protocol is not designed to recruit prisoners. Such proactive reviews address the possibility of subjects becoming prisoners, and may avert the need to either terminate the involvement of subjects who become prisoners or re-review the protocol as a prisoner protocol. Although all required determinations per Subpart C cannot be made in these situations, because the details of the penal facility are not known, the IRB may make the determination that the proposed research is permissible for prisoners. Some of the subpart requirements relate to recruitment within the prison which would not be applicable for these situations; others such as effect of participation on parole decisions would have to be made after a subject becomes a prisoner. In cases where the IRB reviews a protocol in this manner, the approval letter should include a statement that the IRB should be advised via the modification module that such a situation has occurred. The Board can then consider the other items.

Each Board that reviews research involving prisoners will have at least one prisoner representative, i.e., a member or alternate who is or was a prisoner, or who has the appropriate background and experience to represent the rights and welfare of the prisoners. All protocols that will recruit prisoners as subjects will be reviewed by a prisoner representative. When a convened Board reviews research involving prisoners, if the prisoner representative is present at the meeting, he/she will count toward quorum for these protocols. The reviewer form for prisoner research (Working Practice Document #94) will be completed for each review by the prisoner representative.

In addition to its other responsibilities prescribed in these Written Procedures, the Board shall approve research involving prisoners only if it finds that all requirements described in 45 CFR 46.300 (Subpart C) are met.

Human subjects research may involve prisoners as subjects only if the Board has approved the research, considering the above requirements, and the proposed research involves solely research permitted per the federal regulations.

For research involving prisoners, the definition of minimal risk is different than for research not involving prisoners, in that the risk is relative to that encountered in the daily lives of healthy individuals. The following definition of minimal risk will be applied to research involving prisoners:

- the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

The Board will determine that the research under review represents one of the categories of the research permissible under 45 CFR 46.306(a)(2).

Any research involving prisoners that the IRB determines not to represent one of the categories of research permissible under 45 CFR 46.306(a)(2) and that is not federally supported shall have a separate special panel review conducted at CU. The panel will be established by the IRB office and will include individuals with appropriate scientific and ethical expertise to review the given

research project. IRB approval of such research may not proceed without approval from the special panel.

Details of the IRB review for any research project involving prisoners that is federally-supported or conducted will be given to the ED or AD promptly after review, with a draft letter for submission to OHRP. The ED, AD, or designee, will prepare a report for submission to OHRP to satisfy the certification requirements described in 45 CFR 46.305(c).

6. Review of Research involving Children (45 CFR 46, Subpart D)

Children are a vulnerable population and, as such, require additional protections when they are research subjects. At the same time, children should not be denied the opportunity to enroll or the prospective benefits of participating in research.

Federal regulations require that:

a. children be included in certain research activities unless there is a justification for excluding them; and

b. additional precautions be taken when children are research subjects, depending on the degree of risk involved in the research.

NIH policy, which guides the conduct of much human research due to funding relationships, has similar requirements.

The regulations also set forth requirements for obtaining parental permission and, where appropriate, assent by the children themselves. The CU IRBs review research that involves children in consideration of Subpart D of the applicable HHS and FDA regulations, New York state law, and institutional policy. When appropriate, requirements for involvement of minors in research postulated by the New York City Administration for Children's Services (ACS), and/or Department of Education, are also considered. Working Practice Document #107, Research involving Children, provides additional information.

Information provided by the investigator regarding level of risk, prospect of direct benefit (when applicable), assent and parental permission, and inclusion of wards/foster children is evaluated by the IRB, which may concur with the investigator's determinations, make alternative determinations, or impose additional requirements.

Use of the Subpart D Reviewer Form (Working Practice Document #100) helps to ensure that all necessary elements are considered by the IRB reviewer.

a. Determination of Risk/Benefit Category

When a Board (or qualified reviewer for research that is eligible for expedited review) reviews research involving children, it will be determined which of the risk/benefit categories described in 45 CFR 46 (Subpart D) and 21 CFR 56 (Subpart D) the research fits into, whether assent will be required, the manner in which assent will be obtained, if required, the requirements for parental permission or approval of waiver thereof, and the appropriateness of the inclusion of wards/foster children if their involvement is proposed for research that involves greater than minimal risk with no prospect of direct benefit. The IRB will consider information provided by the research team in the Child Involvement section of the RASCAL submission. The Board's (or reviewer's, for research that is eligible for expedited review) determinations will be entered into the minutes for the meeting at which the research was reviewed, if full Board review is indicated, or in the IRB record, in the case of expedited reviews. Concurrence or disagreement with the information provided by the researchers, and basis for the latter, should be included in the documentation of Subpart D findings.

The four possible categories of research involving children are:

1) 45 CFR 46.404; 21 CFR 50.51: Research not involving greater than minimal risk.

   "Minimal Risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

   The IRB, or designated expedited reviewer, will provide the basis for the determination of minimal risk; if there is concurrence with the PI's assessments as entered in the Child Involvement section, a notation to this effect will be sufficient.

   The IRB, or designated expedited reviewer, may determine that the permission of one or both parents is required for research in this category, and will determine whether assent for some or all minors is required.

2) 45 CFR 46.405; 21 CFR 50.52: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

   For research to be approved under this category, the Board must find that:

   a) the risk is justified by the anticipated benefits to the subjects; and

   b) the relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by available alternative approaches.

   The IRB, at a convened meeting, will provide the basis for the determinations of greater than minimal risk and prospect of direct benefit; if there is concurrence with the PI's

assessments as entered in the Child Involvement section, a notation to this effect will be sufficient.

The IRB may determine that the permission of one or both parents is required for research in this category, and will determine whether assent for some or all minors is required.

3) 45 CFR 46.406; 21 CFR 50.53: Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

   For research to be approved under this category, the Board must find that it meets the requirements of 45 CFR 46.406 and 21 CFR 50.53, as follows:

   a) The risk represents a minor increase over minimal risk;
   b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   c) The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the subject's disorder or condition;
   d) Adequate provisions are made for soliciting and documenting assent of the children; and
   e) Adequate provisions are made for soliciting the permission of both parents of each child unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. (45 CFR 46.407 and 408).

   The IRB, at a convened meeting, will provide the basis for the determinations of greater than minimal risk and no prospect of direct benefit; if there is concurrence with the PI's assessments as entered in the Child Involvement section, a notation to this effect will be sufficient.

   The permission of both parents is required for research in this category, unless one parent cannot reasonably provide permission, as allowed per Subpart D. The assent of the minors involved is required unless the Board determines that some or all are not capable of providing assent.

4) 45 CFR 46.407; 21 CFR 50.54: Research not fitting into the aforementioned categories which presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

   The IRB, at a convened meeting, will provide the basis for its determinations regarding risk level and potential for direct benefit; if there is concurrence with the PI's assessments as entered in the Child Involvement section, a notation to this effect will be sufficient.

If the research is supported by HHS jurisdiction, and falls in this category, it cannot be performed without review by the Secretary of the HHS as outlined in 45 CFR 46.407.

Research under FDA jurisdiction that falls in this category cannot be performed without review by the Commissioner of Food and Drugs as outlined in 21 CFR 50.54.

The respective IRB staff will prepare a request for panel review promptly after the IRB review, and will provide such to the ED or AD. The ED, AD, or designee will prepare a report for submission to OHRP to request a panel review as described in 45 CFR 46.407 or 21 CFR 50.54, as applicable.

Research in this category that is not federally funded and does not involve FDA-regulated products will be reviewed by a special panel convened by the IRB office to make the determinations that would be considered by HHS or FDA when evaluating research in this category.

The permission of both parents is required for research in this category, unless one parent cannot reasonably provide permission, as allowed per Subpart D. The assent of the minors involved is required unless the Board determines that some or all are not capable of providing assent.

b. Assent Determination

After the Board makes the risk/benefit determination, they must consider the issue of child assent, as described in 45 CFR 46.408(a) (Subpart D). The Board must decide whether assent is necessary, and also whether and how it will be documented if it is necessary.

Among the formats the Board may consider are the following:

1) waiver of assent;
2) determination that the children lack the ability to provide assent;
3) verbal assent, without documentation;
4) verbal assent, with documentation by the investigator and/or the legally authorized representative(s);
5) written assent form, with subject signature; or
6) subject signature block on consent form (for older children only).

The federal regulations do not require that assent be sought from children starting at a specific age, but that their assent should be sought when, in the judgment of the IRB, the children are capable of providing their assent. IRBs are to take into account the ages, maturity, and psychological state of the children involved (see 45 CFR 46.408(a)).

When the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary (45 CFR 46.408(a)).

c. Inclusion of Wards in Research

Special protections must be considered whenever children who are wards of the state or any other institution, agency, or entity are considered for inclusion in research that is greater than minimal risk with no prospect of direct benefit. Of primary concern are consent issues, i.e., who has authority to enroll a child who is a ward in research. Responsibility for ensuring that appropriate individuals provide permission rests with the PI, and must be in compliance with applicable statutes and the process described in the protocol that was approved by the IRB.

Federal regulations do not require special provisions for wards enrolled in research that is either minimal risk or greater than minimal risk with the prospect of direct benefit. However, the Board may impose additional requirements if the research and/or status of the child(ren) warrant additional safeguards. New York state laws and New York City Administration for Children's Services (ACS) policies will be considered during review of research that involves wards.

Wards may only be included in research that is greater than minimal risk and does not offer the prospect of direct benefit (45 CFR 46.406 or 45 CFR 46.406) when such research is either related to their status as wards, or conducted in a facility at which most of the children are not wards.

If it is proposed that wards will be enrolled in research that is greater than minimal risk and does not offer the prospect of direct benefit, an advocate or advocates who will serve to ensure the best interests of each child are being upheld must be appointed, in addition to obtaining permission from any other individual acting on behalf of the child, e.g., as guardian or in loco parentis. One individual may serve as an advocate for more than one child.

The CU policy, "Research Involving Children" (Working Practice Document #107), provides detailed information regarding the protections required when children are subjects in research.

7. Review of Research involving Other Vulnerable Adults

When all or some of the subjects in proposed research are vulnerable adults, and their vulnerability stems from factors other than pregnancy or incarceration, the Boards will ensure that additional protections are included where necessary to uphold the principles of respect for persons, justice, and beneficence. Specific requirements for the inclusion of pregnant women and prisoners are described elsewhere in these written procedures.

Adults may be considered to be vulnerable for a variety of reasons, including but not limited to:

a. impaired cognitive capacity, either temporary or permanent;

b. economic or educational disadvantage;

c. inability to speak or understand English;

d. medical condition;

e. relationship to researcher.

When the Boards find that the subjects in a research protocol are vulnerable, the Boards will consider additional safeguards on a case-by-case basis (21 CFR 56.111(b); 45 CFR 46.111(b).

For studies involving the possibility of consent by legally authorized representatives for adult subjects, the Boards must consider how it should be determined that a subject is capable of providing his/her own consent, who may legally provide consent if the subject is not capable, and the issue of subject assent. The Boards must determine whether assent is necessary, and how it will be documented if it is necessary.

The IRB must first consider whether the research must be done with the particular group of vulnerable subjects identified in the protocol. If yes, appropriate justification needs to be made for the inclusion of these subjects in any research that will not directly benefit these subjects; this is especially important for those studies that present greater than minimal risk of harm. Even with such justification, additional safeguards should be included to minimize the vulnerability of such individuals. These may include assignment of a research partner or the involvement of a consent form monitor.

8. Review of Research involving Non-English Speaking Subjects

The Belmont Report identifies "justice" and "respect for persons" as two fundamental ethical principles that must underlie the conduct of all human subjects research. The principle of justice requires that the burdens and benefits of research are equitably distributed. The principle of respect for persons requires that "adequate standards for informed consent are satisfied" so that subjects are provided with sufficient meaningful information to decide whether they want to enroll in a research study.

In the review of a protocol the IRB will evaluate the "special populations" information entered in RASCAL by the research team and determine the number or percentage of non-English speaking subjects that are expected to be enrolled. Determinations will be made regarding the need for translation of study instruments and consent documents, in accordance with federal regulations and the CU IRB policy, "Enrollment of Non-English Speaking Subjects" (Working Practice Document #101). This policy also defines acceptable translators and describes the short form consent process, which utilizes verbal consent when a non-English speaking subject is unexpectedly encountered.

9. Review of Research involving International Sites

IRB review of international research raises additional considerations related to obtaining local knowledge of applicable laws, institutional commitments and regulations, standards of professional conduct and practice, cultural norms, and local community attitudes. Physical, social and psychological risks may vary from those in the New York City communities within which the Columbia campuses reside, i.e., the area "local to" the CUMC and CU-MS IRBs. . Assessing the risks and benefits of research conducted internationally may raise challenges if there is not adequate knowledge of the local setting or population to be included. Care must be taken to ensure that the cultural norms of the host country are respected and that the participants will not suffer adverse consequences from participation, such as being subjected to retaliation from local authorities or the local community.

Research projects that take place outside the United States require compliance with Columbia policies and the relevant laws of the host country. International research must also comply with 45 CFR 46 or equivalent standards, such as the 1993 Council of International Organization of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization (ICH) standards, or the 1998 Medical Research Council of Canada Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans.

It is important for researchers to provide information to address these considerations and for the IRB to gain sufficient knowledge of the research locale to accurately assess the risks and benefits of participation and to provide appropriate protections to subjects. Use of consultants is both acceptable and encouraged.

The IRB must consider the following in addition to the review requirements described in Section VI, "IRB Review of Research" and in other relevant sections of this document:

a. The research protocol should generally be designed to address an issue characteristic of the local setting, or conditions that affect the local setting, particularly in developing countries. If the research is greater than minimal risk, then the research should be designed to provide potential benefit to the subjects and/or to the local community. If a research study is not designed accordingly, the investigator should provide satisfactory justification as to why the study is proposed to be conducted in the given setting(s).

b. In an effort to gain knowledge of the local setting, the IRB should consider the most appropriate means of obtaining this information. The type of research, level of risk, study population, location of the research and whether collaborative efforts are involved are all factors that will affect the means of obtaining the knowledge of the local setting.

   For all international research studies, researchers should provide details of the local context within the protocol to provide a basis for the IRB review.

   The IRB may obtain local knowledge from literature, documentation, or available written information, or by inclusion of a consultant knowledgeable of the local setting, in accordance

with OHRP guidance (IRB Knowledge of Local Research Setting, August 1998). For review of minimal risk studies, this level of knowledge may be adequate.

For greater than minimal risk studies, efforts should be made to obtain review and approval from an ethical review committee that is local to the study site or has particular knowledge of the local setting. One source for identification of potential international ethical review committees or IRBs is the list of IRBs registered with ORHP at: http://ohrp.cit.nih.gov/search/asearch.asp#IORG.

IRBs should recognize that international ethical review committees which are affiliated with an institution may not be willing to review research conducted by investigators outside their institution. Access to local ethical review committees may be facilitated when CU researchers collaborate with researchers at the local institution.

The local ethical review committee or IRB should comply with the IRB composition requirements of 45 CFR 46.107 or 21 CFR 56.107, as applicable. In order to increase efficiency, review and approval by the local ethics committee or IRB should usually be obtained after review by the CU IRB or designated IRB on the FWA.

If review by a local human research ethics committee cannot be obtained for greater than minimal risk research, the IRB review must include consultation by an expert who is independent of the research team and is familiar with the local site's culture and norms. The research team may refer such an individual to participate in the review by the convened CU IRB.

c. Obtaining informed consent in accordance with 45 CFR 46 and 21 CFR 50 in certain international settings may raise challenges due to a difference in the norms of the host country. The process for obtaining and documenting informed consent must comply with U.S. regulations and with Columbia policy.

   If the legal age of an adult differs in another country from NY State Law (e.g., 18 years of age), the IRB should accept the local age of majority when considering who may provide their own consent.

d. When consent and recruitment documents have already been translated into a language other than English, the researcher should provide a copy of the document in English, a copy in the language to be used in the foreign location, and certification from an appropriate individual that the translated version of the document is complete and does not contain information that is not presented within the context of the approved English version of the document.

   When the CU IRB-approved informed consent document in the local language is reviewed by an international IRB or ethics committee, the local approved consent document should be back-translated into English by an appropriate individual who will certify that the resulting English version and the local consent document are consistent in content, style, and level of readability.

e. When the research will be conducted in an institution or organization such as a school, business, or hospital that is not otherwise involved in the research, a letter(s) of agreement should be submitted from the appropriate official(s) (e.g., government officials, school officials, community officials, chief executive officers, etc.) indicating that the research protocol, and any and all instruments to be used, have been reviewed and that the study is acceptable to be conducted in the institution or organization. The letter of agreement must be on letterhead stationary and carry an original signature, or otherwise meet acceptable professional standards for a signed document.

f. The research study should provide a plan for oversight of the research that will be conducted in an international setting, particularly when the CU research staff will not be present at the foreign site.

g. The research study should provide a plan for data collection, protecting the confidentiality of the data, and transport of the data back to CU, or elsewhere in the U.S. or another region.

   1) If data will be collected by an individual(s) other than those on the Columbia research team, that (those) individual(s) must be identified and letters of agreement to protect confidentiality should be presented to the IRB. If the non-Columbia researcher(s) will have access to the data for research purposes, the extent of the access should be specified.
   2) Methods for assuring anonymity and/or confidentiality of all data must be specified, particularly if the analysis will occur away from CU.
   3) Processes for transporting data from the international location to CU, with particular reference to protecting the confidentiality of the data while in transit, must be addressed.
   4) If personal health information with identifiers will be transmitted to the U.S., HIPAA requirements must be addressed.

h. If the research study will collect tissues or any other biological samples, the study should provide a plan for the storage and use of the samples, and a plan to protect confidentiality of the samples. If the samples will be transported back to CU or the U.S., the protocol must provide a plan for shipment of the samples that is in accordance with both the local country and U.S. regulations and policies.

   Unsterilized specimens of human and animal tissues (such as blood, body discharges, fluids, excretions or similar material) containing an infectious or etiologic agent require a permit in order to be imported (USPHS 42 CFR 71) to the U.S. Details on the regulatory requirements, process for obtaining a permit, and shipping and handling of such tissues can be found on the CDC website at: http://www.cdc.gov/od/eaipp/.

   If the material being imported has been rendered sterile (e.g., radiation or chemical treatment) and is known not to contain infectious agents for humans, a permit is not required for importation.

The IRB recognizes that there are instances for which parts of the guidance cited above for international studies would be inappropriate, such as with ethnographic research, both domestic

and international, where researchers observe, interact and may live with subjects in their native environment, often for long periods of time. Research that presents concerns that are unique to a population and its culture would, by necessity, require careful consideration by the IRB and the researcher as to how best to protect the rights and welfare of the subjects.

10. Review of Research in Emergency Care Settings

Emergency research refers to the study of acute, life threatening clinical situations. Often, informed consent from the subjects is not feasible because the subject lacks the capacity to provide their own consent (e.g., unconscious) and/or there is insufficient time because treatment must be promptly administered. The conduct of planned research in life-threatening emergent situations requires special consideration by the IRB, including consideration of whether consent may be waived. The specific conditions under which prospective consent of the subject may be waived for planned emergency research are provided by 21 CFR 50.24; the FDA-DHHS Harmonized Rule on Waiver of Consent for Emergency Research permits application of the FDA regulations to planned emergency research situations that do not involve an FDA regulated drug, medical device, or biologic.

If waiver of consent is proposed for those subjects who are not capable of providing consent, and do not have a legally authorized surrogate present, the research plan must include not only public disclosure of the study to the community in which the research will be conducted, but also community consultation. The purpose of the community consultation is to assess whether members of the local population at large would approve of the conduct of the emergency research, i.e., whether they are in favor of such procedures being performed on them if they were in a particular emergency situation. The community consultation should include individuals that represent the targeted subject population that will be enrolled in the study, and must be completed before IRB approval to enroll subjects is provided. It is recommended that the research team meet with the IRB staff to discuss the plan for community consultation prior to its initiation.

The plan for the emergency research study, including the plan for community consultation and public disclosure, must also be approved in advance by FDA if the research involves an investigational or FDA-approved product. If the emergency research study is federally-supported or conducted and does not involve an investigational or FDA-approved product, approval must be obtained from OHRP (on behalf of the DHHS Secretary). The plan must be submitted to the FDA under an emergency IND/IDE by the sponsor or PI responsible for the IND/IDE. The community consultation and the public disclosures, however, generally do not have to be completed prior to submission for FDA approval.

The IRB may approve the study prior to FDA approval of the IND/IDE. When this occurs, the IRB approval will specifically restrict enrollment of subjects as appropriate until the IRB receives notice of FDA approval of the IND, and all outstanding concerns have been adequately addressed.

a. Emergency Research Consent Waiver

The Boards may waive the requirement for informed consent for research involving emergency medical situations if it finds and documents that the requirements of 21 CFR 50.24, which include review and approval of the proposed waiver by FDA, are met. FDA review addresses the requirement in NYS law that consent may only be waived, for activities that meet the NYS definition of medical research, if the activity is subject to federal oversight.

In order to approve an emergency research consent waiver, the Boards shall find and document, with the concurrence of a licensed physician who is a member of, or consultant to, the IRB and is not otherwise participating in the clinical investigation, that:

1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

2) Obtaining informed consent is not feasible because:

    a) Subjects will not be able to give informed consent because of their medical condition;

    b) The intervention under investigation must be administered before consent from the subject's legally authorized representative is feasible; and

    c) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

3) Participation in the research holds out the prospect of direct benefit to the subjects because:

    a) Subjects are facing a life-threatening situation that necessitates intervention;

    b) Appropriate animal and other pre-clinical studies have been conducted, and the information derived from those studies and related evidence supports the potential for the intervention to provide a direct benefit to the individual subjects; and

    c) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

4) The clinical investigation could not practicably be carried out without the waiver.

5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative for consent within that window rather than proceeding without consent. The investigator will summarize the efforts

made to contact legally authorized representatives and make this information available to the Board at the time of continuing review.

6) The Board has reviewed and approved informed consent procedures and a consent document consistent with 45 CFR 46.116 and 21 CFR 50.25. These procedures and the consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The Board has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph 7(e) of this section.

7) Protection of the rights and welfare of the subjects will be provided, including, at least:

   a) Consultation (including, where appropriate, consultation carried out by the Board) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn.

   b) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits.

   c) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results.

   d) Establishment of an independent data-monitoring committee to exercise oversight of the clinical investigation.

   e) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window, a family member of the subject who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the Boards at the time of continuing review.

8) The application to the IRB clearly identified the procedures and environment in which subjects would not be able to provide informed consent.

The Board will ensure that there are procedures in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member:

1) of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document;

2) that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If a legally authorized representative or family member is informed about the clinical investigation, and the subject's condition improves such that he/she is capable of providing informed consent, the subject is also to be informed as soon as feasible.

If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

All study related documents are to be retained by the IRB for at least three (3) years after termination of the clinical investigation, and the records shall be accessible for inspection and copying by the FDA.

The Board will require that a separate Investigational New Drug Exemption (IND) or Investigational Device Exemption (IDE) will be obtained by the sponsor or the investigator, even for marketed products.

The Board will promptly notify in writing the investigator and sponsor when it determines that it cannot approve an emergency consent exception study. The notice shall include the reasons for the disapproval.

The Board may require additional protections for subjects in an emergency research consent waiver study as appropriate.

11. Review of Research that involves Stem Cells

Research that involves stem cells must be reviewed by the University Stem Cell Committee prior to review by the IRB. In cases where the Stem Cell Committee determines that the research does not meet the criteria in 45 CFR 46 to be considered "human subjects research", additional review by the IRB is not required. Review by the IRB of research that involves stem cells will be conducted in accordance with the IRB Review Criteria described in 45 CFR 46 and additional criteria identified in Section VI.B., "IRB Criteria for Review", items 8 through 10, of these written procedures.

E. Review of Specific Types of Documents

1. Review of Recruitment Material

Any item that is intended to be used to encourage a potential subject to consider volunteering for a research study must be reviewed and approved by the IRB before being used**.** The FDA Guidelines indicate that advertising is considered to be an extension of the informed consent process, and thus subject to Board review. Refer to the FDA Information Sheet, "Recruiting Study Subjects", for additional information.

The IRB defines advertising as any research-related information that will be seen or heard by a potential subject before he or she has read and signed a consent form for the study. This means that advertising may include:

- Printed items in newspapers, magazines, flyers, posters, etc.
- Radio announcements
- TV productions or commercials
- Video presentations
- Internet postings
- Web pages
- Informational brochures
- Letters to potential subjects
- Imprinted items (notebooks, bags, etc.)

The IRB will review:

- The information contained in advertisements.
- The mode of their communication.
- The final copy of printed advertisements.
- The final audio/video taped advertisements (or script thereof).

Advertising materials for new protocols that are submitted with the study materials will generally be included in the initial full Board or expedited review.

Advertising material submitted after initial approval of research will generally be reviewed by expedited review. The Board member who is conducting the expedited review may approve the material, require modifications before approval, or refer the proposed materials to the full Board for consideration.

The IRB will ensure that advertisements and recruitment materials:

- Do not state or imply a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the protocol.
- Do not include exculpatory language.
- Do not emphasize the payment or the amount to be paid, by such means as larger or bold type.

- Do not promise "free treatment" when the intent is only to say subjects will not be charged for taking part in the investigation.
- Are limited to the information prospective subjects need to determine their eligibility and interest, such as:
  - The name and address of the investigator or research facility.
  - The purpose of the research or the condition under study.
  - In summary form, the criteria that would be used to determine eligibility for the study.
  - A brief list of participation benefits, if any.
  - The time or other commitment required of the subjects.
  - The location of the research and the person or office to contact for further information.

For FDA-regulated research, the IRB will ensure that advertisements and recruitment materials:

- Do not make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that were inconsistent with FDA labeling.
- Do not use terms, such as "new treatment," "new medication" or "new drug" without explaining that the test article was investigational.
- Do not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it had been approved for marketing.

Approved recruitment material will be stamped with the IRB approval stamp. In some instances, when recruitment materials will be commercially produced or for other reasons, it may be difficult to stamp. In those situations, the IRB may stamp one copy for documentation, and accept a process whereby the stamped copy is retained by the researcher for documentation of IRB approval, but the actual documents may be produced and distributed without the stamp on each copy.

The manual approval stamp will indicate the IRB number, the date of approval and expiration, and the initials of the person stamping the document.

Board review of advertising that will be presented as audio or video advertising will involve both scripts and copies of the tape prepared according to the script. Actual tapes must be submitted for approval following approvable review of the scripts.

No deviation from the approved script is permitted without prior IRB review and approval.

2. Review of Funding Documentation

In accordance with the requirements of 45 CFR 46.103(f), documentation of funded procedures will be reviewed and required for all federally funded projects. This material will be reviewed by the IRB to (at a minimum) ensure that all funded procedures are included in the research protocol, evaluate relationships among collaborators to determine necessary approvals, and confirm key personnel.

Verification of IRB approval will be obtained by pre-award departments of the University prior to creation of an account for award funds.

3. Review of Investigator Brochure

The Investigator Brochure supplied by corporate sponsors will be reviewed by the Primary Reviewer, to facilitate evaluation of risks and benefits through an understanding of the mechanism by which the investigational product acts, preclinical and animal data, and the intricacies of the study design. Review of the Brochure will occur during both initial and continuing reviews, and when a modification includes revision of the document. (Working Practice Document #8).

4. Review of Payments to Participants

The reasons for which individuals decide to volunteer for research participation vary widely. In no case, however, should an individual be induced to accept significant risk for research purposes because of the monetary payment they may receive. The IRB, in its review of payment schedules, must ensure that any monetary payment or other form of compensation is fair, and that elements of coercion or undue influence are not present.

When developed with consideration for the burden or expense that participation may involve, compensation may be justifiable. It may be appropriate, for example, to compensate individuals who participate in research studies for their time and effort, or for transportation expenses. Token acknowledgment of the participants' contribution to science may also occur in the form of payment, provided it is reasonable. For studies that do not offer the prospect of direct benefit, it may also be appropriate to provide reasonable compensation to induce enrollment. In general, such inducement would only be appropriate for minimal risk protocols.

Payment should generally be pro-rated, i.e., distributed evenly among visits, when more than one study visit is involved. If particular visits are significantly longer than others, an uneven distribution may be acceptable if justification is provided. Individuals who withdraw prior to completing all study visits should receive the compensation allotted for all visits that were completed.

Completion "bonuses" may be acceptable if reasonable, i.e., not so large that average participants are compelled to continue study procedures simply to obtain the bonus.

Monetary compensation for children requires special consideration. In general, small age-appropriate books or toys are preferred for young children; cash or a gift certificate of a reasonable amount may be appropriate for older adolescents. The IRB will consider the age of the children and types of study procedures when compensation to minors is proposed.

The IRB will determine that:

- The amount of payment and the proposed method and timing of disbursement is neither coercive nor presents undue influence.
- Credit for payment accrues as the study progresses and is not contingent upon the subject completing the entire study.
- Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.

The following are prohibited:

- Payments to professionals in exchange for referrals of potential subjects ("finder's fees").
- Payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") unless they are judged not to interfere with providing prospective subjects with sufficient opportunity to consider whether to participate and do not increase the possibility of coercion or undue influence on investigators or subjects.

Terms of all payments to participants should be explained during the consent process, and clearly stated in consent documents.

VII. IRB Convened Board Meetings: Organization and Management

A. Schedule of Meetings

Regularly scheduled meetings of each Board are held, with additional meetings scheduled as necessary. The schedule of meetings is available on Columbia's IRB website.

B. Packet Preparation

Members of the Board to which a protocol is assigned have electronic access to all submitted materials for any given event via RASCAL. As necessary and/or requested, Board members are provided with an electronic or paper hard copy of specific materials, determined by type of event, as described below.

When Board members will be relying on an electronic or paper copy of materials that will be reviewed at a convened meeting, IRB staff prepare the packets for distribution approximately one (1) week before the meeting. Details of the packet preparation process are included in Working Practice Document #21.

Each packet includes a copy of the preliminary agenda, administrative notes and copies of the previous meeting's minutes, if the Board has elected to review minutes other than online in RASCAL. If changes have been made after the Board packets have been distributed, members will be notified in advance of of the meeting whenever possible. Copies of the material related to the new items may be distributed at the meeting, although it may have been distributed by email prior to the meeting. Alternatively, the members may be notified of the new items by email and asked to access the material in RASCAL.

1. Initial Review

a. Every packet at a minimum includes a copy of the protocol Data Sheet, Study Description Data Sheet, Notes field affiliated with the event (which includes pre-reviewer notes), and proposed informed consent documents, for each new review request. Copies of advertising and recruitment materials submitted with the initial review request are also included in the packet.

b. Board members receive copies of correspondence between the Investigator and the IRB related to the protocols under review.

c. The assigned primary reviewer(s) for each new review item and the Chair receive, in addition to the material distributed to all members, the Investigator Brochure (or other relevant background information on the investigational article), sponsored project proposal (e.g., grant application and/or sponsor's protocol), research measures, and other supporting documentation, as appropriate.

2. Continuing Review

a. Every packet at a minimum includes a copy of the Data Sheet, Study Description Data Sheet, Notes field affiliated with the event (which includes pre-reviewer notes), informed consent documents, and Renewal Information form.

b, The assigned primary reviewer(s) and the Chair for each continuing review item receive, in addition to the material distributed to all members, a copy of the summary of unanticipated problems, reports from data safety and monitoring units, if applicable, subject complaints, relevant communications with the site and any other new supporting documentation.

3. Modification

a. Every packet at a minimum includes the Data Sheet (which includes the modification summary), Study Description Data Sheet, Notes field affiliated with the event (which includes pre-reviewer notes), and informed consent documents, if they have been modified since the previous submissions.

b. The assigned primary reviewer(s) for each modification and the Chair receive, in addition to the material distributed to all members, a copy of all new supporting documentation submitted with the modification request. These may include, but are not limited to, modified research measures, adverse event reports, revisions to the investigator's brochure, new funding proposals, and reports from data and safety monitoring units.

4. Unanticipated Problem Report

a. Every packet at a minimum includes the Report of the Unanticipated Problem, Notes field affiliated with the event (which includes pre-reviewer notes), and supporting documentation attached by the researcher.

b. The assigned primary reviewer(s) for the event and the Chair receive, in addition to the material distributed to all Board members, a copy of the Data Sheet, and current Informed Consent Forms.

C. Primary Reviewer Assignments

Events that require review by the convened IRB or are eligible for expedited review will be assigned to a primary reviewer. The Chair may elect to serve as the primary reviewer or designate this responsibility to another qualified Board member.

Details of the primary reviewer process may be found in the Process section (Section V.F.) of these written procedures.

D. Voting Requirements

No official action may be taken at a convened meeting unless a quorum is present either in person or via teleconference, and at least one non-scientist is present. Quorum is defined as more than one half of all voting members listed on the IRB roster. The IRB will ensure and document that a quorum is present for review of each event that requires full Board review.

A motion that is seconded, then carried or denied by a majority of the voting members present is required for acting on approvals, deferrals to Chair (referred to as "pending" in RASCAL), deferrals to Board (referred to as "returned" in RASCAL), suspension, and acknowledgement (where applicable). The Chair is a member of the IRB, therefore, he/she counts towards quorum and his/her vote is counted.

The Board does not have to vote to "defer", as an action in RASCAL (i.e., table review until a meeting in the future), a protocol that is on an agenda but is not reviewed due to time constraints, absence of the primary reviewer, loss of quorum or other administrative causes.

A member who has a conflict of interest with respect to the research under consideration (e.g., member of the research team, has financial conflict of interest related to sponsor of the study) may not vote on any action related to that research project. The member will also not count towards the quorum for that study. When necessary to ensure adequate expertise and/or understanding of the research question, a member with a conflict of interest, such as a member who is a PI or holds other status on a research project, may present the study to the Board and answer the Board's questions prior to recusing him/herself and leaving the meeting room for the rest of the discussion and vote for that study.

E. Minutes

1. Recording of Minutes at the Convened Meeting

The minutes for a convened Board meeting must contain sufficient information to comply with regulatory requirements and to serve as the documentation of attendance and actions taken at the meeting.

Assigned IRB staff will be responsible for preparation of the minutes, and will follow the standard Board guidelines, described in Working Practice Document #102. The minutes will, at a minimum, clearly show the following:

a. Date and time of the meeting;

b. Identification of the individual who served as Chair, attendance and voting status of members/alternate members (and for whom each alternate served), attendance of staff and guests, and for guests, the purpose of their attendance;

c. Any changes in attendance (people called away, coming in late, etc.) and voting status; this should include the names of IRB members who leave the meeting because of a conflicting interest along with a statement that a conflicting interest is the reason for the absence;

d. Agenda categories brought before the Board, and clear identification of each item and/or investigator the Board considers;

e. For each item reviewed:

   1) Title and PI;

   2) Name of primary reviewer(s);

   3) A summary of discussion of controverted issues, with resolution;

   4) The basis for requiring changes in or disapproving research;

   5) Any additional conditions required by the Board that may be satisfied after approval of the project but must be adequately addressed before approval of the withheld item is provided, (i.e., receipt of approved Certificate of Confidentiality before a consent form may be released, or completion of educational requirements before an individual may participate in the research);

   6) A clear indication of the Board action taken for each item with a statement of the vote, the number voting for, against, and abstaining, and total number voting;

   7) Statement that IRB review criteria articulated in 45 CFR 46.111 and 21 CFR 56.111 have been met (if action is "approved", or "pending");

   8) Determination of risk level for new protocols, and those events for which the risk level has changed since the last review (if action is "approved", or "pending");

   9) For initial and continuing review, the approval period.;

   10) Waivers (e.g., some or all elements of informed consent, documentation of informed consent, parental permission) that are approved, and the basis for the waiver.

f. For items that are returning to the Board after having been deferred back to the Board, a statement of the area(s) that required significant revision and/or the area(s) of primary concern;

g. For research involving minors, the applicable category of research per HHS and FDA regulations, as applicable, the basis for the determination, requirements for parental permission and assent, requirements for documentation of assent, determination of number of parents who must provide permission, and when applicable, conditions for enrolling wards in research that is greater than minimal risk with no prospect of direct benefit;

h. For research involving pregnant women and fetuses, a statement that the research meets the criteria for allowable research involving pregnant women, the basis for the findings, and consent requirements;

i. For research involving prisoners, a statement that the research meets the criteria for allowable research for prisoners, the basis for the findings, and documentation of review by a prisoner representative;

j. For research involving other vulnerable adults, additional protections as determined by the Board;

k. For research involving devices that are not approved by the FDA, a statement that the IRB has determined whether the test product is a significant risk device or a nonsignificant risk device; if the determination is significant risk, an IDE will usually be required;

l. For emergency research when informed consent will not be obtained, reference to 21 CFR 50.24 (exception to informed consent requirement), basis for determination that the requirements of 21 CFR 50.24(a)(1-7) are satisfied, and summary of the IRB review of plans for community consultation per 21 CFR 50.24(b);

m. Summary of discussion of noncompliance incidents and other new or old business items.

2. Board Approval of Minutes

Minutes that have been approved by the Chair are distributed to Board members in their meeting packets, or members are notified by email that the minutes have been approved, with instructions for reviewing the minutes in RASCAL and/or an attached copy of the minutes. Minutes are ratified, or revisions requested, as applicable, by the full Board at a subsequent meeting of the Board.

3. Notification of Board Action

The Board notifies the investigator and IOs (and the sponsor, when appropriate) in writing of its actions in approving, disapproving or requiring changes to (in order to approve) research.

Investigators are notified electronically via RASCAL correspondence. Hard copy letters of approval (Working Practice Document #93) and disapproval (Working Practice Document #96) letters are also generated and forwarded to investigators; at CUMC this is routine for all protocols while at CU-MS, generation of a hard copy approval letter is predicated by a request from the study team. Hard copy letters may be signed by a Manager, AD, or ED.

A disapproval notice shall include the basis for the disapproval and provide an opportunity, generally within a 30-day timeframe, for the investigator to respond to the Board in person or in writing regarding its action. The Board will consider the response prior to finalizing the disapproval.

A summary of the number of items reviewed, compliance matters, and controverted issues is included in the cover memo (Working Practice Document #104) that accompanies the minutes when forwarded to the IOs.

4. Appeal of IRB Decision

If the Board decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in writing. In general, a 30-day timeframe in which to respond will be imposed.

There is no regulatory authority for appeal of Board decisions in suspending or terminating approval of research.

VIII. Record Retention and Documentation

A. Records Maintained

All required records and reports specified by applicable federal regulations and these written procedures (45 CFR 46.115; 21 CFR 56.115) are retained in RASCAL and/or in IRB files (a paper file may serve as retention of records as a back-up or for some records that were not uploaded in the RASCAL system).

Documentation of the following IRB activities and regulatory requirements is maintained:

1. Copies of all research proposals reviewed;
2. Scientific evaluations, if any, which accompany the proposals;
3. Approved consent documents;
4. Statements of significant new findings provided to subjects as required by 45 CFR 116(b)(5), 21 CFR 50.25(b)(5);
5. Copies of all modifications or amendments to protocols;
6. Reports of unanticipated problems;
7. Records of continuing review activities;
8. Progress reports submitted by research investigators;
9. Minutes of IRB meetings (see Section VI: Meeting Preparation and Follow Up);
10. IRB review (e.g., in Notes, correspondence, IRB reviewer form), including actions taken by reviewer or Board, approval and expiration dates), determinations (e.g., waiver of informed consent, waiver of documentation of informed consent, Subpart-specific determinations), restrictions (e.g., suspensions, contingencies), and reviewers;
11. Correspondence between the IRB and the research investigators;
12. List of Board members and their alternates identified by:
    a. Name;
    b. Earned degrees;
    c. Representative capacity;
    d. Indications of experiences such as board certifications, licenses, etc.;
    e. Information sufficient to describe each member's chief anticipated contributions to the IRB deliberations;
    f. Any employment or other relationship between the member and the institution;

10. Board member curriculum vitae, appointment letters, and other relevant correspondence involving member service;
11. Emergency use reports;

12. Reports submitted to the IRB regarding injuries to subjects;
13. Exemption determinations, including category of exemption;
14. Reviews conducted under an expedited review process, including category, actions taken by the reviewer such as returns or approval, and required determinations;
15. Investigations related to allegations of noncompliance;
16. Not-for-cause audits;
17. Interactions with federal regulatory agencies regarding compliance matters.

B. IRB Files

Each protocol is assigned a unique number and is maintained in an individual file within RASCAL. The RASCAL electronic record is considered to be the official IRB file. Copies of some submissions or documents related to submissions may also exist in paper form in file cabinets located in the IRB office area. Original hard copy IRB records may not be removed from the IRB office without the written approval of the ED or AD.

C. Record Retention Term

Records relating to a specific research activity, including research records collected by investigators must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.

Protocol-specific IRB records, and IRB records that are not protocol specific (e.g., minutes, rosters, or correspondence not related to a specific study), in RASCAL will be maintained within the system and on backup media throughout the time that RASCAL is used as Columbia's protocol submission and tracking system. If RASCAL is superseded by another electronic system, and all data are not transferred to that system, the RASCAL data will be retained electronically for a period thereafter of at least three years.

Protocol-specific hard copy IRB records that are not in RASCAL will be maintained on-site for a minimum of 6 months after termination or withdrawal of the protocol. They may then be transferred to long-term storage off-site.

Hard-copy IRB records that are not protocol specific (e.g., minutes, rosters, or correspondence not related to a specific study) will be maintained on-site for at least 6 months after the period in which they are current. They may then be transferred to long-term storage off-site.

Documents transferred to off-site storage will be retained for at least 3 years.

D. Confidentiality of Records

IRB records, including records relating to specific research protocols, are kept confidential to the extent possible and allowed by law. However, authorized representatives of sponsors, federal regulatory agencies, University officials, IRB staff, University staff with legitimate access, and IRB Board members may review, inspect, and/or copy records.

E. Inspection of Records

IRB records are accessible for inspection and copying by authorized representatives of the Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), and other agencies, when appropriate jurisdiction exists, at reasonable times and in a reasonable manner (45 CFR 46.115(b); 21 CFR 56.115(c)). Requests for photocopying and release of any IRB records must be received in writing and approved by the ED or AD.

F. Off-site Storage of IRB Files

Hard copy study files may be stored offsite if they meet the following qualifications:

- The study has been terminated and no submissions for the file are pending a review; or
- The study was disapproved; or
- The study was never approved due to failure to respond satisfactorily to IRB requests.

Off-site storage location: Morgan Manhattan
1405 Jerome Ave.
Bronx, NY 10452
Telephone: 718-538-3976
Fax: 718-538-3978

The storage space is alarm-protected and fireproof. Retrieval of a file is generally completed within 1-2 business days after a request.

Shipment or retrieval of any item to or from off-site storage may occur only after approval is provided by the ED or AD. A record is kept in the IRB office of all files transferred to off-site storage.

IX. Oversight Monitoring

The Columbia HRPP assures oversight monitoring of human subjects research by various means, such as:

1) continuing review of the research by the IRB and brief inquiries with investigators or research records following concerns raised by IRB review;
2) IRB review of unanticipated problems involving risks to subjects or others;
3) data and safety monitoring by either an internal or external committees;
4) compliance oversight initiatives including for-cause and not-for-cause investigations;
5) additional reviews, investigations or monitoring by the Research Pharmacy, Radiation Safety Office (RSO) or Institutional Biosafety Committee (IBC); and
6) additional reviews conducted by either the Clinical Trials Office (CTO) or Research Administration (RA).

Furthermore, quality improvement efforts provided by the IRB office, as described in Section XI, serve as additional mechanism to provide oversight monitoring of human subjects research.

A. Continuing Review

As described in Section VI.C.6, continuing review serves a key role in oversight monitoring of all human subjects research that is not exempt. By reviewing the progress of the study during the past approval period, the IRB receives information and insights to the risks associated with the study and the quality of study management. Through these insights the IRB is often able to make determinations that additional oversight monitoring may be necessary and in such cases, may refer a given study to the Compliance Oversight Team for further investigation or audit.

IRB staff and members are mindful of IRB expiration dates during the review process, particularly when subjects are actively participating and an interruption in the conduct of study procedures may pose an increase in risk to those subjects. While the IRB may not extend the IRB approval period without additional review, consideration may be given to allowing the continued participation of enrolled subjects to prevent harm or an increase in risk of harm. Investigators are advised to submit renewal requests sufficiently in advance of the expiration date to ensure sufficient time for review.

B. Review of Unanticipated Problems Involving Risks to Subjects or Others (including Adverse Events)

The review of adverse events and other unanticipated problems provides an important role in the oversight of human subjects in research. The process for IRB review of unanticipated problems is described in sections VI.A.4 and VI.C.2. Timing of and action subsequent to IRB review of unanticipated problems depends on the severity, relationship to the test article, and whether the event occurred under the auspices of Columbia or at another site that relies on another IRB for

review of the event(s). Depending on these criteria, the CU IRBs review the events either promptly or at continuing review.

C. Data and Safety Monitoring

The IRB will review a data and safety monitoring plan for certain research studies as described in Section VI.B.6. During the course of studies conducted by Columbia (either at Columbia or elsewhere), the IRB will review and/or solicit information from the applicable data and safety monitoring board or committee to address any relevant IRB concerns. The IRB will also rely on the data and safety monitoring boards and/or the sponsor to provide assessments of the adverse events or other unanticipated problems involving risks to subjects or others that may occur during the study.

D. Reviews or Monitoring by the Research Pharmacy, Radiation Safety, or Institutional Biosafety Committee

For monitoring of human subjects research providing specific risks from radiation, hazardous materials (including research with human organs, tissues, or fluids), or investigational drugs and devices, the IRB may also rely on additional oversight provided by the Research Pharmacy, Joint Radiation Safety Committee, the Radioactive Drug Research Committee, Radiation Safety Office (which provide administrative support to both committees) or the Institutional Biosafety Committee. The Columbia HRPP provides for effective partnering and communication between each of these committees or offices and the IRB as appropriate. The IRB may rely upon either compliance oversight or oversight monitoring by these other groups either in lieu of, or as an adjunct to the oversight monitoring provided by the IRB.

To enhance the oversight of human subjects research/clinical investigations involving ionizing radiation, communication between the IRB and radiation safety committees (i.e., JRSC and RDRC) will include:

1) For any study involving human subjects and an investigational radiopharmaceutical that is not conducted under an IND, the IRB will forward a copy of the IRB approval to the RDRC.

2) For any study involving human subjects and an investigational radiopharmaceutical that is conducted under an IND or a radiographic procedure that is not standard practice (or the frequency of the procedure is greater than standard practice), the IRB will forward a copy of the IRB approval to the JRSC.

3) For continuing review of any study covered in items 1 or 2 above, the IRB will forward a copy of continuing review (i.e., renewal) IRB approval to the RDRC or JRSC, as appropriate.

4) For any unanticipated problem involving risks to subjects or others (UP) related to an investigational radiopharmaceutical, radiation therapy or a radiographic procedure, the

IRB will forward the UP report along with the IRB review of the event to the RDRC or JRSC, as appropriate.

5) Any IRB approval of a modification or amendment to a protocol that involves or affects procedures involving ionizing radiation will be forwarded to the RDRC or JRSC, as appropriate.

E. Reviews by Clinical Trials Office or Research Administration

The Clinical Trials Office, Research Administration (at CUMC) and Office of Sponsored Programs (at CU-MS) each provide additional oversight of human subjects research during their routine review of contracts or grants. Each of these offices will communicate with the IRB office to resolve issues regarding IRB review of human subjects research. Issues commonly addressed range from assuring IRB review of grants as appropriate, review of subcontracts by the appropriately designated IRB, resolution of conflicts of interest issues, payment for research related injuries, and miscellaneous issues that could be identified during their routine review of contracts or grants.

F. Compliance Oversight

Compliance oversight procedures cover two types of Noncompliance: Research Noncompliance and IRB Noncompliance.

"Research Noncompliance" means Noncompliance by anyone other than the ED or any member of the IRB staff or the IRB (in his/her capacity as such).

"IRB Noncompliance" means Noncompliance by the ED of the IRB or any member of the IRB staff or the IRB (in his/her capacity as such).

For purposes of IRB policy, "Noncompliance" means a failure to comply with University policy or applicable federal and state laws, regulations and policies governing the protection of human subjects in research.

A response to an allegation of Noncompliance consists of three phases, each of which is explained in more detail in the CU "Noncompliance with Human Subject Regulations" policy (Working Practice Document #89):

Inquiry: the gathering of preliminary information and fact-finding to assess whether an allegation has substance and, if so, whether an Investigation is warranted (an "Inquiry"); this phase should be brief and not involve a substantive analysis of any information, but should determine whether the PI is actually conducting, or has conducted, the study, whether the information presented in the allegation appears to be potentially relevant, affiliation of the source of the allegation with the University, and whether any documents should be sequestered;

Investigation: following an Inquiry, the further investigation of facts with respect to whether Noncompliance has occurred (an "Investigation"); and

Outcome: following an Investigation, the determination as to whether Noncompliance has occurred and what corrective actions, if any, are required (an "Outcome").

Related concepts of appeal, reconsideration, and notification to regulatory agencies are also addressed in the CU "Noncompliance with Human Subject Regulations" policy (Working Practice Document #89), as are guidelines for safeguards for the complainant and respondent, and measures to ensure confidentiality, preserve evidence, and sequester documents.

X. Education & Training

A. Research Community

The CU IRB considers ongoing education of IRB staff, Board members, and investigators to be of utmost importance towards effective protection of human subjects research conducted under the auspices of the institution.

The following media are used to keep the research community at Columbia up to date on matters related to human subjects research:

1. Web site;

2. Email listserv;

3. Group meetings with research personnel and other individuals involved in the Human Research Protection Program.

To the extent possible, documentation of educational activities supported by the IRB and/or attended by staff and IRB members will be maintained. See Working Practice Document #105 for a list of educational events.

To facilitate communication between the IRB administrative office and the research community, the IRB maintains one or more email accounts for receipt of inquiries related to the protection of human subjects. The account(s) are monitored, and responses are generated, by IRB staff. Analysis of the inquiries that are received may identify areas in which additional education is necessary.

B. Board Members & Chairs

All incoming Board Members must attend an IRB orientation upon being appointed to the IRB. This session includes exposure to the Belmont Report, relevant federal regulations, and IRB policy.

The following material is distributed or made available to all newly appointed Board Members:

1. Columbia University IRB Policies and Procedures (http://www.cumc.columbia.edu/dept/irb/policies/index.html#irb);
2. OHRP IRB Guidebook (http://www.hhs.gov/ohrp/irb/irb_guidebook.htm);
3. "Protecting Study Volunteers in Research" (Dunn & Chadwick).

All Board Members and Chairs are required to have the following certifications:

1. Appropriate Columbia University Good Clinical Practices course;
2. Columbia University HIPAA course.

Perusal of the OHRP Assurance Training modules (http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp) is also recommended to IRB Chairs and members.

Hard copy documentation of the above and any other relevant certifications is maintained by the IRB staff.

All members are exposed to ongoing educational opportunities such as regional or local IRB conferences and CU IRB sponsored events. An educational retreat is held periodically for all Board Members and staff. Continuing education information is distributed to the Board members on an ongoing basis, and is posted on the IRB web site for future reference.

All Board members and Chairs will have access to publications related to the protection of human subjects in research, such as:

1. Newsletters;
2. Relevant articles;
3. Literature.

The performance of IRB Chairs and members is evaluated periodically as described in Working Practice Documents #113 and 114.

C. Administrative Staff

The IRB administrative office holds regular education sessions for IRB staff. These sessions address all facets of human subjects protections.

The following material is distributed or made available to all IRB Staff:

1. Copy of the Columbia University IRB Policies and Procedures (http://www.cumc.columbia.edu/dept/irb/policies/index.html#irb);
2. OHRP IRB Guidebook (http://www.hhs.gov/ohrp/irb/irb_guidebook.htm;
3. "Protecting Study Volunteers in Research" (Dunn & Chadwick).

All IRB Staff are required to have the following certifications:

1. Columbia University Good Clinical Practices course;
2. Columbia University HIPAA course.

All staff have access to other educational opportunities, as resources allow. These include:

1. Attending local and national IRB conferences;
2. Access to the CITI online training program;

3. Access to publications related to the protection of human subjects in research, such as:
    a. Newsletters;
    b. Relevant articles;
    c. Literature.

All eligible staff are encouraged to pursue the Certified IRB Professional (CIP) status, which is obtained through successful completion of a comprehensive exam administered by the Council for Certification of IRB Professionals (CCIP). Details regarding eligibility, the content of the exam, and registration may be obtained from the CCIP website: <http://www.ptcny.com/clients/CCIP>.

IRB staff at the officer level are evaluated formally at least once per year as per the recommendations of the Human Resource department at Columbia. The job descriptions for all IRB officers includes a requirement to stay abreast of both changes to existing relevant regulations and statutes, and those that are newly implemented.

Support staff are regularly provided with feedback from their supervisors regarding performance. All staff members are encouraged to attend informational sessions relative to the protection of human subjects, whether such events are presented by the IRB office or by another entity.

D. Researchers

All key personnel involved in human subjects research are required to have the following training:

1. Appropriate Columbia University Good Clinical Practices certification:
    a. Protection of Human Research Participants for Patient-oriented Clinical Research (CUMC);
    b. Protection of Human Research Participants for Epidemiology and Social and Behavioral Sciences (CUMC);
    c. Protection of Human Subjects (CU-MS);
2. Columbia University HIPAA certification;
3. If children will be involved as subjects, the CITI Biomedical Research with Children online module.

The IRB administrative office holds regular educational sessions for all researchers. Educational opportunities are also available through departmental and divisional meetings.

Investigators are apprised of new or revised policies, procedures, and regulations by email notification via the IRB listserv and posting on the IRB website.

Explanation for required changes (in correspondence transmitted when submitted materials are returned to the investigators) provides another avenue for education on a protocol-specific basis.

XI. Quality Assurance and Improvement

The CU IRB is committed to the improvement of the quality, performance and efficiency of its reviews and internal processes, and those of University research teams in regards to the conduct of research with human subjects. Towards these ends the IRB administrative office has implemented various processes to monitor performance of the staff and review boards. The focus of these activities is on providing optimal customer service by enhancing the ethical conduct of research while also meeting or exceeding the needs of our research community. Customers are defined as Principal Investigators, research staff, human subjects, and any other individuals or entities involved with the Columbia Human Research Protection Program (HRPP).

Quality assurance and improvement activities are administered primarily through the IRB Central Review Team (CRT), which is responsible for collecting and processing data that enables the IRB office to quantify and assess performance and efficiency of the IRB and the University researchers. In addition to data collected manually for assessment, RASCAL reports are generated as necessary by the CRT, AD, or ED.

A. Internal Assessment and Improvement Initiatives

The CRT, at the direction of the ED and AD, prepares and forwards reports to the ED, AD, and IRB Managers for review. Reports may be prepared on a regular schedule, such as the retinue of weekly reports described below, or on an ad hoc basis. Reports to be prepared will be determined based on institutional and office needs.

The CRT is responsible for the primary analysis of data and other information that is collected on the quality and performance of the overall IRB operation. Recommendations made by the ED, AD, and IRB Managers for specific types of reviews or events, based on these data analyses, are forwarded to the relevant individuals within the operation. Recommendations and comprehensive reports prepared by the CRT are forwarded, as appropriate, to the IRB Executive Committee.

Knowledge gained from the measures described provides input for educational efforts and provides an opportunity to improve a process or policy.

Weekly reports include the following:

1. Pre-Review Tracking report: Measures the number and timeliness of pre-reviews of new protocol submissions by the IRB professional staff (distributed to ED and AD only).
2. Administrative C Queue report: Measures the number and timeliness of responses from individual IRB reviews to the researchers in the RASCAL system (distributed to IRB Chairs, Managers, ED and AD).
3. Resubmission Review by Team report: Measures the number and timeliness of reviews of the responses from researchers to previous IRB correspondence or action (distributed to IRB Chairs, Managers, ED and AD).

4. Delayed IRB Reviews by Team report: Identifies individual reviews by IRB members that are pending for longer than two weeks but less than one month, and longer than one month (distributed to IRB Chairs, Managers, ED and AD).

Monthly and quarterly reports of pre-reviews of new protocols, approval of IRB meeting minutes, and IRB turnaround time are also provided.

When necessary, assessment of IRB performance data will be conducted by individuals outside of the IRB staff who have expertise in statistical analysis.

B. External Assessment and Improvement

Various procedures will be conducted to assess the impact of IRB performance on researchers, to identify areas for which education or training efforts should be implemented, to ensure that study procedures are conducted in accordance with the protocol that was approved by the IRB, and to gain an understanding of the services the IRB may provide which may facilitate the ethical conduct of research.

1. Researchers and research subjects will be surveyed periodically to determine levels of satisfaction and to identify areas in need of improvement.
2. Informed consent processes will be randomly monitored.
3. Unanticipated Problem reporting will be monitored for timeliness of the reporting and compliance with the Columbia Reporting to the IRB of Unanticipated Problems policy.
4. When appropriate, quality action teams, comprised of PI(s), research staff, members of the IRB staff (e.g., clerks, administrative aides, Manager), IRB Chair(s), IRB members, and a member of the RASCAL Information Technology team will be formed to brainstorm solutions to problems and implement planned improvements.
5. Processes, whether newly instituted, recently improved, or ongoing, will be monitored continuously for their effectiveness.

XII. Subject Outreach

A. Information for Potential Subjects

Information regarding subject rights, and issues that an individual should consider prior to enrolling in a research study, are distributed throughout clinical areas at CUMC and are posted on the IRB website: <http://www.cumc.columbia.edu/dept/irb/>

The IRB Office maintains a relationship with Community Board #12, which represents the Washington Heights area surrounding CUMC. The primary objective for this interaction is to remain informed about services that the IRB may provide to the community, and to inform the community about services that the IRB may provide.

The IRB also endeavors to be present at local health fairs and other community events where information about the rights of participants in research may be disseminated.

B. Subject Advocacy Program

A program to assess the experiences of subjects who participate in research conducted by University personnel is currently under development. Proposed modules for an online program would collect data from subjects on:

- The informed consent process;
- Medical care that was received;
- Interactions with medical personnel;
- Interactions with support staff;
- Logistics of visiting CUMC;
- Communication about the progress of the study;
- Contact with the IRB office.

Feedback would then be provided to the various entities in the Human Research Protection Program, to enable each unit to improve their procedures as necessary to encourage further participation.

Appendices

Appendix I	The Belmont Report; Ethical Principles and Guidelines for the Protection of Human Subjects of Research
Appendix II	Department of Health and Human Services (HHS) Regulations for the Protection of Human Subjects
Appendix III	United States Food and Drug Administration (FDA) **r**egulations for the Protection of Human Subjects
Appendix IV	Department of Education FERPA (Family Educational Rights and Privacy Act) regulations
Appendix V	New York State Laws 2440/441
Appendix VI	New York State Law Article 7, Section 79-1 Confidentiality of Genetic Tests
Appendix VII	AAHRPP Accreditation Standards
Appendix VIII	International Conference on Harmonization (ICH) "Guidance for Industry-E6 Good Clinical Practice: Consolidated Guideline"
Appendix IX	HHS/FDA List of Expedited Review categories

Working Practice Documents

Sorted Numerically

2	Unanticipated Problems (including adverse events) Reporting Policy
4	Definition of RASCAL status terms
5	Cooperative Agreements Overview Guidance for Staff
6	Oncology Protocol Review Guidelines - 7/10/03 email from GG
7	Oncology review update - 8/23/03 email from GG
8	Investigator Brochure Review Guidelines - 7/30/03 email from GG
9	Exempt Continuing Review Guidelines - 11/26/03 email from GG
10	Informed Consent Policy
13	Principal Investigator Policy
16	Audio/Videotaping of Human Subject Policy
17	Audio/Video Addendum to Consent Form
18	Investigational Drugs: Use and Control - NYP
20	Pre-review Guidance and format - 3/21/05
21	Package organization
24	Pre-review Process flow chart
34a	Reviewer form: New protocols (Biomedical)
34b	Reviewer form: New protocols (Behavioral)
35	RASCAL General Information Screen
61	Revised RASCAL renewal form
64	How to Prepare RASCAL Submission (RASCAL's)
66	RASCAL Emergency Use General Information form
67	RASCAL Termination Report
69	RASCAL Modification Information Form
70	RASCAL Submission Manual - draft JEE
71	RASCAL Consent form creation - MIM handout
76a	Conflict of Interest disclosure form - CUMC annual
76b	Conflict of Interest disclosure form – CU-MS annual
89	Noncompliance Policy
91	IRB staff job descriptions
92	RASCAL Investigational Products section
93	Approval letter templates
94a	Reviewer form: Subpart C (Prisoner) research (for staff reviewer)
94b	Reviewer form: Subpart C (Prisoner) research (for Board reviewer)
95	RASCAL correspondence distribution list
96	Disapproval letter template
98	CU Petty Cash Policy
99	Emergency Use letter of acknowledgment template
100	Reviewer form: Subpart D (Minors) research
101	Enrollment of Non-English Speaking Subjects
103	CU Guidance for obtaining consent during labor
104a	Cover memo for forwarding minutes to CUMC and NYP IOs
104b	Cover memo for forwarding minutes to CU-MS IO
105	List of educational initiatives

107	Research with Children policy
108	Email from GG, "Addition of new expedited review category in RASCAL"
109	Reviewer checklist: IRB review criteria
110	Renewal pre-review form
111	Termination pre-review form
112	Guidance: Modifications – What Constitutes a Substantive Change?
113	Process for evaluating IRB Chairs
114	Process for evaluating IRB members
115	Policy on Privacy and Research (HIPAA)
116	Procedures related to HIPAA review
118	Processes for review and monitoring of protocols subject to IAAs
127	CU IRB memo November 15, 2005 re recognition of service by IRB members
128	Use of Students as Study Subjects
160	IRB Contact Information
161	Exceptions to Automatic Consent Form Stamping
162a	Notification to PI, CTO, OFBC of Category A or B device
162b	Notification to PI, CTO, OFBC of Category A or B device (submission instructions)
188	RASCAL UP Report

Working Practice Documents

Sorted Alphabetically

93	Approval letter templates
17	Audio/Video Addendum to Consent Form
16	Audio/Videotaping of Human Subject Policy
76a	Conflict of Interest disclosure form - CUMC annual
76b	Conflict of Interest disclosure form – CU-MS annual
5	Cooperative Agreements Overview Guidance for Staff
104a	Cover memo for forwarding minutes to CUMC and NYP IOs
104b	Cover memo for forwarding minutes to CU-MS IO
103	CU Guidance for obtaining consent during labor
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114	Process for evaluating IRB members
118	Processes for review and monitoring of protocols subject to IAAs
188	RASCAL AE Report

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66	RASCAL Emergency Use General Information form
35	RASCAL General Information Screen
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94a	Reviewer form: Subpart C (Prisoner) research (for staff reviewer)
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61	Revised RASCAL renewal form
111	Termination pre-review form
2	Unanticipated Problems (including adverse events) Reporting Policy
128	Use of Students as Study Subjects

Glossary of Abbreviations and Terms

Abbreviation or Term*	Explanation
AAHRPP	Association for the Accreditation of Human Research Protection Programs
AD	Associate Director, IRB
AE	Adverse event
BB-IND	Investigational New Drug Exemption for biologic
CIP	Certified IRB Professional
CFR	Code of Federal Regulations
COI	Conflict of Interest
Columbia	Columbia University
CU	Columbia University
CUMC	Columbia University Medical Center
CU-MS	Columbia University – Morningside campus
DNA	Deoxyribonucleic Acid
ED	ED, Human Research Protection Program
EU	Emergency Use
Events *	RASCAL term for submissions to the IRB for review (e.g., new protocol, modification, renewal)
EVPR	Executive Vice President for Research at Columbia University
Executive Committee *	Committee comprised of IRB Chairs, ED, AD, and VPRO at Columbia University
FDA	United States Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HCP	Health Care Proxy
HDE	Humanitarian Device Exemption
HHS	US Federal Department of Health and Human Services
HIPAA	Health Information Portability and Accountability Act
HRPP	Human Research Protection Program
HUD	Humanitarian Use Device
IAA	IRB Authorization Agreement
IBC	Institutional Biosafety Committee
ICH	International Council for Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug
IO	Institutional Official
IO-CUMC	Institutional Official for Columbia University Medical Center
IRB	Institutional Review Board
IT	Information Technology
JRSC	Joint Radiation Safety Committee at Columbia University
LAR	Legally Authorized Representative
LOA	Letter of Approval

LOD	Letter of Disapproval
NIH	National Institutes of Health
NSR	Nonsignificant Risk designation for medical device
NY	New York
NYP	New YorkPresbyterian Hospital
OGC	Office for General Counsel at Columbia University
OHRP	United States Office for Human Research Protection
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee at the Herbert Irving Comprehensive Cancer Center at Columbia University
QIP	Quality Improvement Program
RAC	Recombinant DNA Advisory Committee at NIH
RASCAL *	Electronic protocol submission and tracking system at Columbia University
RDRC	Radioactive Drug Research Committee at Columbia University
SR	Significant Risk designation for medical device